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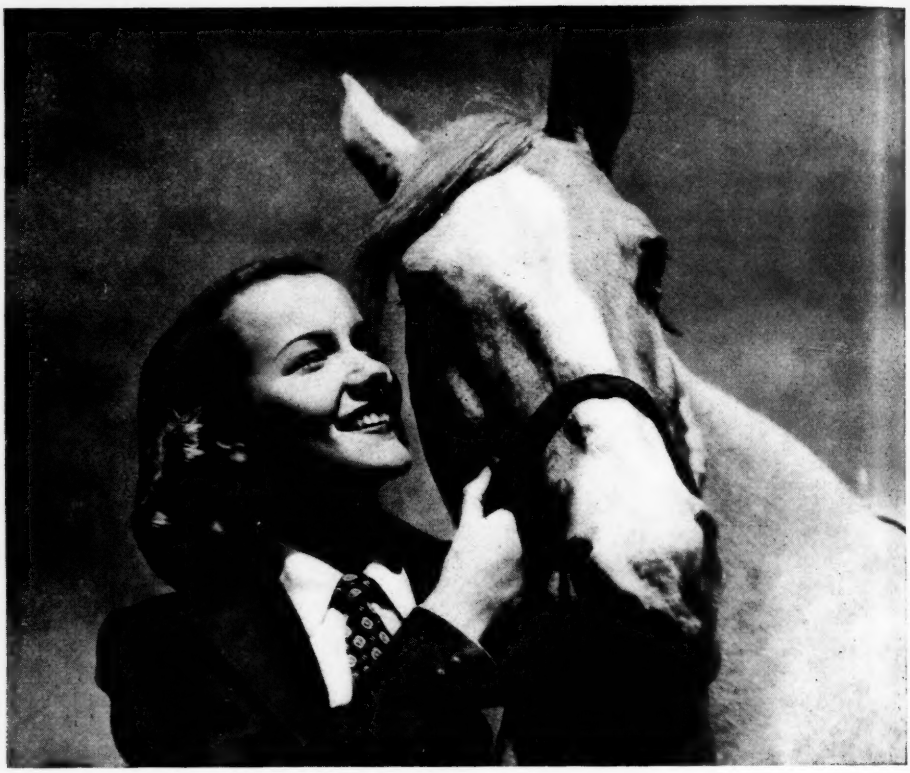

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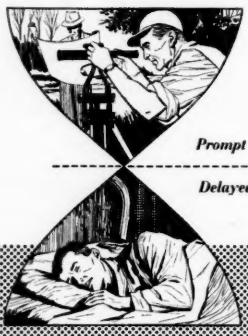


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# MICROSCOPIC OBSERVATIONS OF THE INTRAHEPATIC CIRCULATION OF LIVING GUINEA PIGS BEFORE AND DURING ANAPHYLAXIS

WALTER S. BURRAGE, M.D., and JOHN W. IRWIN, M.D.
With the Technical Assistance of
INA GRAM PETERSEN and PRISCILLA GORDON
Boston, Massachusetts

IN RECENT years there has been a tendency to move the research laboratory nearer to the patient. This trend is a good one, for the ultimate aim of all medical research falls into the following categories:

1. A better understanding of man's anatomy, physiology, chemistry, and psyche.
2. An accumulation of knowledge as to how disease alters these concepts.
3. The development of methods to treat disease successfully on sound scientific grounds.

In 1948, a decision was reached to tackle a problem at a basic level. It was decided to study active anaphylaxis since this is a dynamic reaction which runs its course rapidly. It seemed that one or more of the three great integrative systems of the body—the circulatory, hormonal or neural might be involved in this dramatic reaction.

This paper has two purposes: first, to describe a number of observations on the structure, connections, and behavior of parts of the intrahepatic blood vascular system of anesthetized guinea pigs and, second, to describe the changes in this system during anaphylaxis.

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Dr. Irwin is Research Fellow in Medicine, Massachusetts General Hospital, Boston, Massachusetts.
This investigation was supported in part by Grant H-906, National Institutes of Health, in part by funds from the Allergy Clinic Fund of the Massachusetts General Hospital, and in part by the Mary Dexter Fund.
Presented before the Ninth Annual Congress of American College of Allergists, Chicago, Illinois, April 27, 1953.

## BACKGROUND LITERATURE

Knisely, Bloch and Warner[2] worked for more than a decade studying the intrahepatic circulation of living Amphibia and Mammals. During this time they developed a quartz rod method of transilluminating living tissue so that the small blood vessels of internal organs could be studied with microscopes. Wakim and Mann[6] and Seneviratne[5] with similar methods studied the intrahepatic circulation of living mammals. To our knowledge no one has previously reported on microscopic observations of the intrahepatic circulation of living mammals undergoing anaphylaxis.

## MATERIALS AND METHODS

In these studies healthy guinea pigs were the experimental animals. The animals were sensitized by a 0.5 cc intraperitoneal dose of crude egg white, 1:10 followed by a similar injection on the fifth day. No cavy was used until twenty-one days after the second sensitizing dose. Each animal was anesthetized with intraperitoneal sodium pentobarbital. The initial dose was about 0.045 gram per kilogram, and subsequent doses were administered as required.

Respiratory motions interfered with microscopic observations of the intrahepatic circulation of mammals so it was necessary to abolish them. A modification of the original method of Meltzer and Auer[4] was employed. A tracheotomy was first performed, and into this opening a tapering pyrex cannula was placed. This cannula did not fill more than two-thirds of the tracheal lumen. The cannula was then attached by means of rubber tubing to an oxygen tank, and oxygen was transmitted from the tank at about 0.5 liter per minute. Before reaching the trachea, the oxygen was passed through water contained in a closed flask. The open area between the cannula and the tracheal walls enabled respiratory gases to escape from the lungs. When the positive flow of oxygen was adjusted correctly, all respiratory movements ceased.

Careful surgical technics aimed at preventing loss of blood and tissue trauma were employed to expose the liver. A midline incision through the linea alba from the tip of the xiphoid process to the area of the umbilicus presented the peritoneum. On cutting the peritoneum the liver was exposed. To prevent drying, the liver was immediately covered with gauze pads soaked with mammalian Ringer's solution at 38° C. The guinea pig was then placed on its back on a stand equipped with drains and adjustable legs. The whole preparation was moved to the experimental table, constructed so as to prevent vibration being transmitted to the experimental animal. This table weighed about 500 pounds and was mounted on rubber. A small part of the liver was then uncovered. Two gentle streams of mammalian Ringer's solution at about 38° C were immediately directed onto this exposed area. The temperature of these streams of Ringer's solution was maintained by a constant temperature and circulating bath mounted on an accessory table.

The edge of the liver was transilluminated for observation. Light from a 1000 Watt T-12 G. E. projection bulb was transmitted down a quartz rod with a hollow tip similar to the one described by Hoerr.[1] The bulb and rod were held in position by one of the later quartz rod holders from

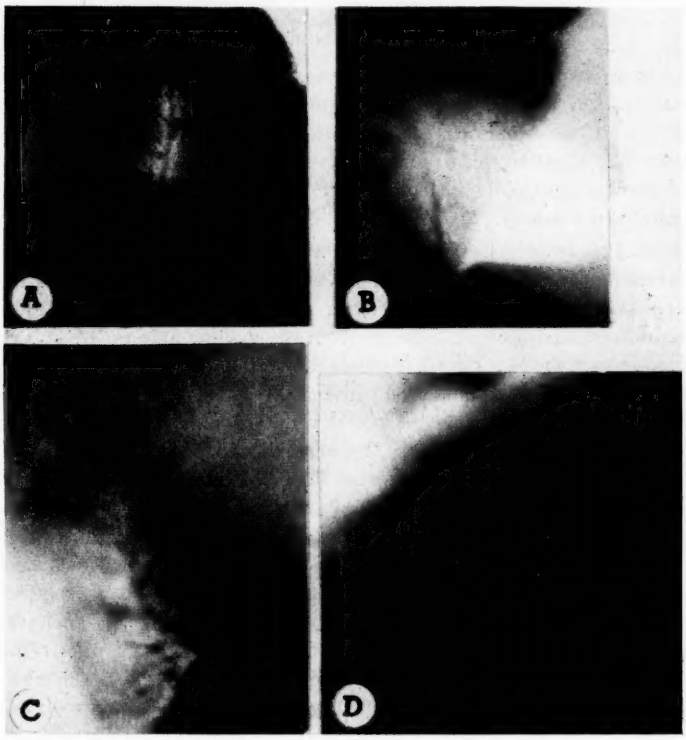


Fig. 1. Photomicrographs

(A) The larger vessels are portal and central venules of approximately 30 to 80 micra in diameter. In the spaces between these vesesls are the honycombing sinusoids of about 15 micra.

(B) The vessel in the center is a portal venule with a diameter of about 50 micra.

(C) The large vessel is a central venule of about 70 micra in diameter. The meshworks formed by sinusoids appear about this vessel.

(D) Two central venules, the smaller one having a diameter of 20 micra and the larger one measuring about 70 micra are seen joining to form a sublobular vein.

Knisely's laboratory having precision adjustments so that the tip of the rod could be moved in the horizontal plane as well as vertically. Ringer's solution at 38°C flowed from the tip of the rod, on which stream rested the very edge of the liver. This stream of Ringer's solution carried away excess heat produced by the light.

In this type of experimental observation microscopes providing clear resolution and multiple magnifications were needed. A stereoscopic Leitz microscope with magnifications up to 150× and a monobjective, monocular, compound microscope with magnifications up to 500× were used for all observations.

## OBSERVATIONS

As in all microscopic fields much was observed at relatively low magnification. On first inspection at magnifications of 48× to 60×, larger vessels were seen marking out distinct areas approximately 2 to 4 mm across. The areas between these vessels appeared to be honeycombed with great numbers of small anastomosing vessels. Photomicrograph A (Fig. 1) visualizes such a field.

Careful study of these areas at higher magnifications up to 500× led to identification of these vessels. Among the larger vessels were found intralobular portal venules. These venules gave off many branches, and the direction of blood flow was always from the main venule to the branches. Photomicrograph B (Fig. 1) shows a portal venule. On occasion a hepatic arteriole was found accompanying the portal venule. This arteriole usually wound itself around the portal venule in an irregular manner and gave off branches. Furthermore, between the arteriole and portal venule shunts were found. The direction of linear blood flow was always from the arteriole to its branches. The flow of blood generally was more rapid in the arteriole than in the venule. Both the portal venules and arterioles gave off branches to the sinusoids which were the small vessels honeycombing the areas. The living hepatic sinusoids appeared as completely lined, hollow, smoothwalled, branching and anastomosing cylindrical tubes. Knisely et al[2] pointed this out and showed that the Kupffer cell was not a star-shaped cell suspended within the sinusoids like a spider in a tube as originally believed. Photomicrograph C (Fig. 1) shows sinusoids. The central venules were among the larger vessels and were quickly identified as blood flow was from the branches into the larger vessel. Central venules united to form sublobular vessels. Photomicrograph D (Fig. 1) shows a central venule.

Months of careful study with magnifications up to 500× led to the suggestion that each of the described vessels possessed independent contractility. The following observations tended to support this contention.

1. All vessels described were seen to contract to such an extent that no blood cells were able to pass.

2. At each end of the sinusoid, in the walls of both the portal venule and central venule, were found opaque areas when the tips of the sinusoids were tightly closed. When the tips of the sinusoids were wide open, no opaque areas were noted.

3. On occasion the lumens of the central and portal venules, hepatic

arterioles, and sinusoids were observed to shut tight at just one portion of the vessel.

During anaphylaxis leading to death, the intralobular hepatic vessels underwent several interesting changes. When the sensitized animal under the described experimental conditions was shocked by an intravenous injection of the specific antigen, it was necessary to work fast for the animal died in a few minutes. Grossly, the liver became larger immediately, suggesting the storage in it of large quantities of blood. Microscopically, a series of events was seen in about the following sequence:

1. The sphincters of the sinusoids at the central venules shut off.
2. The hepatic arterioles contracted.
3. Linear blood flow in the central venules stopped.
4. The sinusoids became engorged with blood.
5. Finally linear blood flow in the portal venules ceased.
6. No open hepatic arterioles were found during anaphylaxis.

In short, a considerable amount of blood accumulated in the liver, confirming the gross appearance of this organ.

## DISCUSSION

We are not the first to have studied the intrahepatic circulation in living animals. Knisely,[3] Knisely, Bloch and Warner,[2] Wakim and Mann[6] and Seneviratne[5] have already done so. All are in general agreement as to the circulatory architecture of the intact liver. Seneviratne, however, did not describe sphincters at the ends of sinusoids. Wakim and Mann found hepatic arteries accompanying central venules with anastomoses between them in the frog, but not in the mammal. The latter observation might suggest that arterial blood might pass through the liver without nourishing tissue about the sinusoids.

The preliminary nature of our present studies does not warrant the drawing of definite conclusions, yet current observations do suggest that storage and immobilization of blood in the liver may prevent its general circulation and thereby its oxygenation, and in this manner be an important factor in anaphylactic shock.

## SUMMARY

1. A method of transilluminating the livers of living guinea pigs deeply anesthetized with sodium pentobarbital and of studying the intrahepatic blood vessels with microscopes were presented.

2. Portal venules, central venules, sublobular veins, hepatic arterioles, arterio-portal anastomoses and arterial sinus twigs were observed in the liver of living guinea pigs. Sinusoids were visualized as hollow branching and anastomosing cylindrical tubes with a continuous lining.

3. All of these vessels of the guinea pig liver lobule showed evidence of independent contractility.

4. Certain changes in intrahepatic circulation during anaphylaxis leading to the storage of blood in the liver lobules of guinea pigs were described.

5. A tentative hypothesis was suggested that storage of blood in the liver might be of importance as a mechanism in anaphylaxis in guinea pigs.

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# HYPOTHYROIDISM IN PEDIATRIC ALLERGY

**WILLIAM A. REILLY, M.D.**
**San Francisco, California**

FROM a long and close experience with hypothyroidism, I feel that the genesis has not been properly understood. The genesis[1] is governed by various combinations of the following factors: The age of onset, the degree of hormonal deficiency and the response of the various end organs (target tissue). Not all of the signs and symptoms are equally developed in all systems of the body. It may take years to develop marked deficiency in a given patient. Usually, as the gland slowly loses normal function, the deficiency progresses slowly and insidiously, and occasionally it is steplike. There may be total remission of the deficiency, but this is rare. Usually remission is partial and temporary.

The effects of age of onset is an interesting factor. The congenitally hypothyroid fetus is maintained by the mother's thyroid substance, which in this country is usually normal in amount and sufficient to develop a normal fetus throughout pregnancy. Such a newborn infant is usually quite normal in length, weight and appearance. The acquired thyroid substance from the mother may not be used up for several weeks or months after birth, so that the usual signs of the deficiency will not be manifested until then. If the baby nurses, the mother's thyroid substance is also obtained thereby. Some of our so-called cases of acquired hypothyroidism are probably congenital deficiencies. Examination of photographs during infancy and beginning childhood reveal the early onset of failure to grow and develop normally, the early appearance of myxedema, et cetera. Only about one-sixteenth of the amount of normal gland is necessary for the usual needs of the body. If the baby is born with a hypoplastic gland, just able to carry on normally, the stresses of infections or the stresses of extra growth, which occur in the first six months, again at two years, again at five to seven years of age, and at puberty, can well be too great. The deficiency then will first manifest itself.

The response of the end organs (target tissues) is significant. Hypothyroidism can affect all parts of the body. However, at a given time not all tissues seem to be deficient or to react equally to a given lack. Some of these tissues, which seemed to be doing normally on a reduced ration of thyroid substance, will at a later time first show deficiency. This may well be due to decreased sensitivity of the end organs, resulting from a variety

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From the University of Arkansas, School of Medicine, Little Rock, Ark.

Presented before the American Academy of Pediatrics in panel discussion, Toronto, Canada, October 21, 1951.

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of factors, particularly infections, growth stresses, and possibly allergic states. Myxedema is not always evident in the early phases of the disease or when it does appear, it may be localized to only certain parts of the body. We have seen it only in the larynx or only about the joints or only as ascites or only as menorrhagia. Some marked hypothyroids even have normal mentality. Anemia may not develop early or until after some duration. I think that hypothyroidism can occur temporarily, and such temporary deficiency can be quite marked at times. Three such patients are in my memory, and one of them, quite recently.

The degree of hormone deficiency is somewhat readily understandable. In athyreosis the deficiency is practically total. It is now known, however, that thyroxine-like substances are formed in tissues elsewhere in the body than in the thyroid gland. There is also always the possibility that a small amount of thyroid tissue may be present in the neck. Our own I-131 uptake studies indicate this. An athyreotic individual will not be able to supply the extra hormone demanded during the stresses of growth and infection. It is interesting the athyreotic requires only 2 to 4 grains of thyroid substance daily, while the obese patient very often requires 5 or more grains daily, for any reduction. In obesity the thyroid function is nearly normal and the extra thyroid substance is calorigenic in its action.

In general, hypothyroidism probably does not occur any more frequently in the allergic state than in the whole childhood population. The indication then for thyroid substance would be the same—that is, the presence of hypothyroidism. However, thyroid substance has some universal systemic effects—it is calorigenic, sympathicotonic, dehydrating, and appetite stimulating. All of these actions appear at times in the allergic patient given thyroid substance.

Usually, many clinicians only recognize hypothyroidism when it is most florid, and this unfortunately is, all too often, the only form taught or written. Hypothyroidism most often occurs in subclinical forms of mild degree. I think, also, that these mild degrees occasionally can last temporarily and not be recognized. Both of these degrees of deficiency probably occur among allergic individuals with the same frequency as in the whole population. With sharp clinical acumen, the physician might be able to detect such mild, temporary degrees of hypothyroidism and his patient can be helped by thyroid substance.

Many chronic diseases, especially if severe enough in childhood, are accompanied by failure to grow well in height, weight and other usual measurements of proper development. As instances, failure of proper growth and development occurs in malformations of the central nervous system, heart, liver, kidneys, et cetera. Also allergic states of long duration and great degree can cause such failure of proper growth and development. Examination of some such children reveals a low basal metabolic rate, definite retardation in epiphyseal development, and other evidences pointing to endocrine and particularly thyroid deficiency. Such

states, when they simulate hypothyroidism may not definitely be due to only thyroid hormone lack. Nevertheless, some of these malnourished and physically retarded children have been known to respond to thyroid substance. This may be particularly true of the chronic malnourished, asthmatic, or eczematous child. I should like to stress again, that this is not a prima facie evidence that mainly the child has hypothyroidism. However, the chronic degree of the allergic condition and its accompanying malnutrition might well suppress activities in the endocrine glands and particularly in the thyroid. Very likely in such states, the thyroid substance may exert a sympathicotonic effect. Another helpful effect is the dehydrating action that occasionally can be induced with thyroid substance when treating overweight eczematous infants. Both effects could be called symptomatic therapy.

Thyroid substance should be used intermittently and as long as there is a noticeable response. The dose may have to be raised to amounts considered excessive. Because primary hypothyroidism may not be present such symptomatic usage of the substance requires high doses, for the tissues are not in great need or very avid for the extract.

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*42nd Avenue and Clement Street,*
*San Francisco 21, Calif.*

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# ATOPIC DERMATITIS CAUSED BY INHALANT ANTIGENS AND ITS IMMUNOLOGIC THERAPY

H. ELIAS DIAMOND, M.D., F.A.C.A.
Bronx, New York

IT IS generally believed that inhalant antigens such as house dust, pollens, or molds are but rarely involved as causative agents in atopic dermatitis. However, in recent years several experienced allergists and dermatologists such as Tuft,[7] Epstein,[2] and Rowe[5,6] reported data which indicate that inhalant antigens do play a significant role in the etiology of atopic dermatitis in adults and children.

In over twenty years of practice in allergy, we were frequently confronted with etiological problems in eczematous dermatoses. In recent years an increasing number of patients have presented themselves primarily for the treatment of atopic dermatitis, and it is noteworthy that the majority of them came upon the recommendation of older patients with respiratory complaints, for whose concomitant dermatoses a successful therapeutic approach had been obtained. Thus from slowly accumulating experience certain concepts were evolved which we believe may be of general interest. These are:

1. A high incidence of eczematous dermatoses is seen among subjects with respiratory allergies, such as hay fever and bronchial asthma.
2. They often improve coincident with the treatment of the respiratory complaints by means of individually adjusted and, as a rule, small doses of extracts from the antigens involved in the respiratory affection.
3. Exacerbations of dermatitis caused by inhalants are observed following the injection of extracts from dust, pollens, molds, et cetera, for the purpose of testing or for therapy.
4. The favorable experience in the treatment of such affections with concentrations of dust, pollens, or mold extracts much smaller than those used in the treatment of respiratory affections. This procedure was developed as a logical consequence of the experiences noted in the preceding paragraphs.

1

Of 236 consecutive new cases seen during the period from January, 1949 to July, 1952, the primary complaint was directed towards the respiratory tract 179 times. Among these, the diagnosis of a concomitant atopic dermatitis was made in twenty-three instances, that is 9.5 per cent of the total.

In the remaining fifty-seven cases of this series, the primary complaint was of dermatologic nature. Among these, the diagnosis of atopic dermatitis was made twenty-three times, of which seven (or better than one out of four) were also suffering from bronchial asthma, allergic rhinitis, or hay fever.

## 2

The improvement of atopic dermatitis coincidental with the immunologic treatment of hay fever, bronchial asthma, or allergic conjunctivitis is exemplified by the following case histories.

*Case 1.*—A. N., a twenty-three-year-old woman typist, was first seen on September 28, 1948. She gave a history of hay fever since the age of six, with typical nasal and eye symptoms which recurred each year. No attempt had ever been made to treat this condition. Her chief complaints at her first visit were itching and redness over the entire body, accompanied by sneezing every morning. She first noticed red areas on her face early in October, 1945, and she attributed this to a new satin dress uniform worn during a parade. In August, 1946, she observed a rash on the lower part of both arms and fingers. It was very itchy and oozed. This continued until the end of September and then disappeared. It recurred in August, 1947, with similar skin manifestations. In August, 1948, the skin condition reappeared, but this time it spread over the entire body.

Objective Findings: There were numerous areas of erythema just above the dorsum of the right wrist. Numerous vesicles were seen in the region of the fingers, face and chest. When ruptured, a colorless fluid exuded. Intradermal testing revealed positive reactions to house dust, and to the pollens of ragweed, timothy grass, plantain, and trees (oak and birch).*

Treatment: Since the etiology for the allergic rhinitis was known, and since the history so clearly noted the occurrence of the rash every August for three consecutive years, treatment was started with antigens of dust, ragweed, and timothy grass in low concentrations. It was noted that there was not only a clearing of the nasal symptoms, but also a parallel improvement of the skin affection. The only medication used was calcium gluconate. The highest dose of ragweed administered was 50 pollen units, timothy grass 600 pollen units, and house dust 0.40 ml of a 1:10 dilution. Treatment was continued until May 3, 1949, when the patient stopped her treatment. At this time all symptoms of itching and weeping of the atopic eczema and nasal symptoms had cleared.

The patient returned on May 23, 1952, with similar skin manifestations to that previously noted, but with bronchial asthma instead of the nasal symptoms. Treatment with smaller doses of the same antigens as previously employed was started. The atopic dermatitis responded much more rapidly than in 1948. Retesting to inhalants and molds revealed a marked reaction to Trichophytin. With high dosages such as 0.02 ml intradermally of 1.30 Trichophytin, the dermatitis of the hand became aggravated for several days. The dose was then reduced to 0.02 ml of a 1:120 dilution and when this still produced a strong local reaction it was further reduced to a 1:480 dilution. The patient is on this dose at present. The hands and bronchial condition remain under control.

*Summary.*—Atopic dermatitis concomitant with hay fever and—four years later—with bronchial asthma were successfully treated by small doses of the antigens involved.

It is of some interest that just as is often observed with pollen, a mold antigen caused an exacerbation when used in the usual diagnostic dilution.

*Case 2.*—I. F., aged thirty-two, wife and daughter of physicians, was first seen on October 22, 1948. She had had hay fever for many years and had received im-

*Extracts of pollens and house dust were prepared by the author. The mold extracts were purchased from the Lederle Laboratories, as were the food extracts used in testing.

munization treatment, but in the past few years her father had suggested antihistaminic drugs instead of specific therapy. Her chief complaint was not the hay fever but a skin affection, namely, marked redness and itching in the cubital fossae. She stated that the eruption began in June, 1948, and had continued unabated. She also noted generalized itching and any close contact with metal, such as a buckle, would produce a localized "dermatitis."

Objective findings: An eruption about two inches in circumference was seen in both cubital fossae. There was erythema, but no oozing or excoriation. Intradermal testing revealed positive reactions to house dust, ragweed, plantain, and timothy grass.

The diagnoses were: (1) hay fever, and (2) atopic dermatitis (also contact dermatitis which is not relevant here).

Treatment was started with low concentrations of ragweed, timothy grass, and house dust. Within a few weeks the atopic dermatitis cleared. At this writing, almost four years later, there has been no recurrence. At no point in the treatment did the dose of ragweed pollen exceed forty-eight pollen units, although the dosage for the timothy extract was slightly higher. The dose of the house dust was 0.25 ml of a 1:10 dilution. The hay fever is well controlled at present. Some nasal symptoms developed in May, 1952, and were treated with small doses of oak and birch pollen.

*Summary.*—In this case of hay fever and atopic dermatitis treatment with low doses of the pollens involved cleared not only the allergic rhinitis but also the associated atopic dermatitis.

*Case 3.*—A. S., aged twenty, a counterman, was first seen on April 3, 1950. His chief complaint was continuous nasal obstruction throughout the year. He stated that his nasal symptoms began August, 1948, with itching and watery lacrimation puffiness of both eyelids, and marked nasal clogging. The condition continued until the middle of September, 1948. He also noticed an eruption on the left elbow and left knee. This had appeared each June for the previous two years and somewhat earlier during the present year. Two years prior to the onset of the nasal symptoms he had undergone nasal surgery for a deviated septum, and the removal of nasal polyps.

Objective findings: Examination of the nose showed pale boggy membranes. Both nares were almost completely obstructed. An eruption was visible in both cubital and popliteal fossae. This was approximately one inch in circumference with no oozing or excoriations. Intradermal testing revealed positive reactions to house dust, ragweed, timothy grass, and birch pollens.

A diagnosis of (1) allergic rhinitis due to dust and pollens, and (2) atopic eczema, was made.

Treatment was instituted for the allergic rhinitis with low concentrations of house dust, ragweed, timothy grass, and birch pollens. Marked swelling occurred in the right arm in which 0.15 ml of a 1:50 dilution house dust and 6 pollen units of ragweed had been injected. Within a period of a week and with similar antigen doses, the nasal symptoms cleared up. There was concomitant improvement of the atopic dermatitis to the point of its disappearance from the cubital and popliteal areas.

When there was a short lapse in treatment the eruption reappeared. Treatment was resumed with gradual improvement of both rhinitis and atopic dermatitis. The patient was then inducted into the armed forces, and it was learned that the eruptions recurred at the army post.

*Summary.*—In this case of allergic rhinitis and mild atopic dermatitis in which treatment primarily directed against the respiratory symptoms caused clearing of the

skin disorder, lapse in treatment was followed by a recurrence of the atopic dermatitis.

Case 4 is an example of the situation where a patient comes to the office primarily with a dermatologic complaint, and where the finding of an allergy of the respiratory tract provides the clue for the management of the dermatosis:

*Case 4.*—H. S., aged seventeen, a college student, was first seen on June 10, 1950, with severe generalized atopic dermatitis. Past history: At the age of nine months, the mother first noticed a rash in the back of the knees. When he was one year old, he developed "heaviness" in breathing. He felt well until the age of five, when he had pneumonia followed by an attack of asthma. For the past few years, attacks of bronchial asthma had occurred only occasionally, the last severe one in December, 1949. In the past few weeks the rash appeared to be getting worse.

Objective findings: The patient wore long sleeves to cover the oozing, excoriated and macerated skin. The face was full of scratches. Intradermal testing revealed positive reactions to house dust, ragweed, plantain, timothy grass, and tree (oak and birch) pollens.

A diagnosis was made of (1) bronchial asthma, and (2) atopic eczema.

Treatment was started with low concentrations of house dust, ragweed, timothy grass, and tree (oak and birch) pollens. Within a few weeks, the bronchial and skin condition showed concomitant improvement. By July 10, 1950 large patches of normal skin were visible. In another three days his face appeared greatly improved. At the onset treatments were given at two or three-day intervals, and as improvement proceeded, the time interval was lengthened. The only internal medication used was calcium gluconate. Treatment was continued until October 10, 1950, with continued improvement in both the bronchial and the eczema conditions. He left for college and treatment was discontinued.

The highest dose of the ragweed did not exceed 7 pollen units. The dosage of the timothy or tree pollens never exceeded 30 pollen units. The highest dose of the house dust was 0.20 ml of a 1:50 dilution.

*Summary.*—A case of severe generalized atopic dermatitis with occasional bronchial asthma was treated with low doses of dust, ragweed, and other pollen extracts, resulting in spectacular improvement of the skin manifestations.

*Case 5.*—C. W., aged eighteen, a girl, was first seen on June 28, 1950, with three separate complaints, namely:

1. Nasal: Explosive sneezing would occur at any time, day or night.
2. Eye: Constant mucous discharge from both eyes, also photophobia and interference with vision due to the swellings of the eyelids. The mouth was also swollen at the same time.
3. Skin: Unbearable itching in the region of both elbows, the face, and the back of the neck. This condition had recurred in the middle of August for a period of fourteen years and would improve in the winter. The patient was severely affected by the constant oozing and intense itching.

Objective findings: There was a stringy, mucous discharge from both eyes, with lacrimation. The mucous membranes of the nose were pale and edematous. The face appeared swollen and there was edema of both eyelids. The lips were also swollen, the upper lip more so than the lower one. There was marked thickening of the skin of the face to the touch. The cubital areas showed diffuse areas of redness with marked loss of pigmentation and induration, which extended down both fore-

arms. Intradermal testing revealed positive reactions to house dust, plantain, timothy grass, and tree (oak and birch) pollens.

Our diagnosis was: (1) allergic rhinitis and conjunctivitis, (2) atopic dermatitis, and (3) angioneurotic edema of the face.

Treatment was started for the mucosal affection which according to the history and the results of skin testing was being caused by pollens and house dust. The only internal medication used was calcium gluconate. The only treatment of the skin consisted of local applications of Burow's solution, a 1:64 dilution.

With extremely weak concentrations of antigens of house dust, ragweed, timothy grass, and tree pollens, there was immediate improvement in both the allergic rhinitis and conjunctivitis, and parallel improvement in the atopic dermatitis. Within a period of three weeks, the itching in the cubital area, face and neck had subsided and the oozing stopped. Immunization was continued with house dust and the aforementioned pollens. A recurrence of the atopic dermatitis took place on September 5, 1950, but no recurrence of the mucosal symptoms (nose or eye) was seen. A second relapse occurred on September 18, 1950, with increased itching in the cubital fossae, but with no evident oozing.

For reasons which will soon become apparent, the further course of the treatment will be described in Section 4.

A similar case was previously reported[5], but it was complicated by the presence of additional dermatoses caused by sensitivity to foods. This is an occurrence which should be kept in mind.

A particularly illustrative case was observed by Dr. A. J. Weil, to whom we are obliged for permission to present Case 6.

*Case 6.*—A. H., aged twenty-eight, a housewife, was first seen January, 1950, with a history of frequent severe attacks of asthma since early childhood. They were more frequent in the summer, but would occur any time of the year. As a farmer's daughter she found out that asthma was elicited when she came near cows or the cow shed. When members of the family, returning from work with cattle, came close to her, an attack was evoked. She also noticed that contact with wool had something to do with the production of asthma. However, neither the avoidance of wool, nor the eventual removal from the farm after her marriage brought relief. The only time she was free of asthma was during her pregnancy. The asthma returned with redoubled severity after her delivery.

In addition, she was annoyed for many years with a chronic severly pruritic skin affection which migrated over the body in frequent exacerbations. It was present always over the flexor side of her arms and legs. In contrast to the asthma, this rash had become aggravated during her pregnancy and at one period became so unmanageable that an interruption of the pregnancy was considered. However, at the time when she was first seen, this complaint was minor in comparison with the asthma.

Objective findings: The nasal mucosa was pale and swollen. Numerous rhonchi were heard all over the lungs. Chest x-ray showed accentuated trunk markings, but no deviation from the normal. Secretions from the nose and bronchi contained numerous eosinophiles. There was a widespread itching rash, particularly of the face, the flexor regions of the arms and legs, and the upper trunk. The co-operating dermatologist, the late Dr. Elizabeth M. Weil, diagnosed this as a chronic dermatitis. Intradermal testing revealed positive reactions to house dust, ragweed, plantain, timothy grass, oak and birch, feathers, sheep's wool and hormodendrum. Advice concerning the avoidance of wool, and the replacement of the feather pillows with

foam rubber was given, and the need for avoidance of places where dust accumulated and those connected with dairying and fowl raising, were impressed upon the patient.

Treatment with house dust and pollens was started and continued at slowly increasing intervals until the present time. Doses above 0.01 ml of the weak dust extract and 20 pollen units of any of the pollen extracts were apt to cause some local reaction and exacerbation of the dermatitis. Therefore the dosage was kept below this level. Ephedrine and epinephrine were required in the beginning, but have not been resorted to during the past two years. Under this regime the asthma gradually subsided. During the pollen seasons there were days when itching of the eyes and stuffiness of the nose were seen, but cleared without treatment in a few days. The only occasions when heaviness and slight wheezing were noted after the first three months of treatment were: (a) house cleaning in attic or cellar, during the first year (however, since 1951, she found that she could expose herself to dust without undue reaction); (b) during occasional visits to the farm; and (c) during a few days in the spring when birch trees outside the bedroom windows were pollinating.

There had been a weight gain of eighteen pounds which had been maintained. The dermatitis was topically treated by the co-operating dermatologist during the first few months. Along with the improvement of the respiratory symptoms, the dermatitis greatly improved so that eventually no local therapy was needed. However, lichenification at the bends of the elbows and face persisted, and occasionally new crops of papulovesicular efflorescences appeared. Considerable experimentation was done, until the attention was focused upon the correlation of these recurrences with the intake of large amounts of milk or ice cream. When these foods were replaced by meat and cereals, the dermatitis finally disappeared. After several months even the lichenification of the face and elbows subsided. At present this patient has a normal skin, except for a few groupings of papules which appear on the same place on the right cheek each time she menstruates. She continues to avoid milk and ice cream in large amounts, but experiences no difficulties with the small amounts of milk and cream present in cake et cetera, and can take some cream in her coffee.

*Summary.*—This is a case of severe asthma and dermatitis. The former could be entirely correlated with a number of inhalant antigens, and brought under control by specific immunologic therapy. The same therapy also greatly improved the dermatitis, but this affection could be completely relieved only when it was realized that an additional factor was involved, namely, sensitivity to milk.

Infection may play a similar role as a factor additional to inhalant antigens, as witnessed by the report of Case 7.

*Case 7.*—B. T., a four-year-old boy was seen on February 12, 1952, with a history of bronchial asthma and a severe weeping, widespread skin affection. Both had first appeared at the age of two years. The asthma was not seasonal, and it became worse after upper respiratory infections. Exacerbations of the rash, however, were observed each year in September. Attempts to find a clue to the cause of the dermatitis by the use of elimination diets recommended by the pediatric allergy department of a metropolitan hospital were unsuccessful.

Objective findings: There was no evidence of any wheezing or rhonchi in the chest on initial examination. Nasal mucosa was slightly pale and edematous. Large areas of skin were indurated, and covered with crusts. There was abundant weeping and in some places bleeding. The rash was worse in the popliteal folds. There were in addition several areas of erythema and induration on the dorsal aspect of the

right elbow and the dorsum of both wrists. The face also showed evidence of scaling and excoriation. Intradermal testing revealed positive reactions to house dust, ragweed, and feathers.

A diagnosis was made of (1) bronchial asthma, (2) atopic dermatitis, and (3) subsequently, of chronic sinusitis.

Treatment was started with high dilutions of house dust and ragweed. Within a period of eight days (four treatments) the weeping rash in the popliteal region had cleared to a great extent. The oozing had stopped and normal skin was seen. The only medication used was calcium gluconate. The patient was temporarily turned over to an associate who inadvertently increased the dose of ragweed from 0.1 to 1 pollen unit. The result was an exacerbation of the rash. The condition was so severe that further specific therapy with the above antigens was interrupted. The possibility that infection might play a role in the cause of the bronchial asthma was considered. By mild suction applied to the nares, a purulent discharge was obtained. The skin affection had become so alarming that immediate hospitalization was required. He was discharged after a week, with improvement of the dermatitis, following treatment with terramycin and wet compresses.

This was followed by treatment of the sinus condition with intranasal penicillin aerosol. In three weeks, the infection of the nose cleared. At this point we resumed treatment of the atopic dermatitis with the very high dilutions of house dust and ragweed. The atopic dermatitis cleared completely, and only a very mild recurrence was noted beginning on August 26, with slight reddening in the popliteal folds, with no itching. The bronchial asthma likewise improved, and the only medication occasionally needed was ephedrine.

*Summary.*—A case of asthma and eczema, in which the course of events clearly indicated that infection played a role. Only when the respiratory infection (sinusitis) was brought under control by antibiotic therapy, did the immunologic treatment give the expected results.

Treatment indicated by the considerations and diagnostic procedures outlined in the preceding paragraphs resulted in satisfactory results in thirty-seven cases of this series. In nine cases no complete observation was possible. In twenty-seven cases, inhalent antigens appeared to be the sole etiologic factors, including four cases where in addition to dust and pollens, sensitivity to molds was involved. In four cases foods appeared to be definitely incriminated, and in two, elimination of respiratory infection was found of importance.

3

After we learned to appreciate the correlation between respiratory allergy and dermatitis, we became aware of the occurrence of the converse phenomenon, namely, the exacerbation of such dermatoses after the therapeutic administration of a homologous antigen. Happenings of this kind have already been described in Case Reports 1, 6, and 7. It is further exemplified by the following case, involving a high degree of reactivity to a mold antigen.

*Case 8.*—M. L., aged nineteen, a girl high school student, was first seen on October 21, 1946, for the treatment of bronchial asthma. Past history revealed that she had eczema as a child. In the early summer of 1944, she developed hay fever. No

treatment was given, and eventually asthma developed in the late summer and early fall of 1946. There was no evidence of dermatitis when she was first seen. Intradermal testing revealed positive reactions to house dust, ragweed, and timothy grass.

Treatment with the above antigens in average doses cleared the bronchial asthma. Treatment was continued perennially for a period of two years. Further treatment was refused after relief of the bronchial condition had been obtained.

While under treatment for the bronchial asthma for some time, the patient called our attention to an occasional redness and itching of the back of both hands. We believed this was a mold sensitivity and with intradermal treatment with 0.02 ml of 1:30 trichophytin, the rash on both hands cleared. Only a few doses of the mold antigen were needed.

She came back for treatment in September, 1951, with typical atopic dermatitis at the bend of both elbows. In addition, there was marked redness and oozing of the dorsum of both hands. There was marked loss of pigment in the region of the cubital fossae. No respiratory symptoms were present.

Since we knew the antigens involved in the bronchial asthma, we tried the same antigens in very low concentrations for the treatment of the atopic dermatitis, namely, house dust, ragweed, and timothy grass. Within a few weeks the affection of the elbows cleared up, but that of the hands became worse. In view of our previous findings of trichophytin sensitivity, we added intradermal injections of 0.02 ml of a 1:30 diluted trichophytin. The next day the inflammatory reaction on the hands was visibly intensified. Therefore, it was presumed that this was an overdosage, and the trichophytin concentration was gradually reduced to 1:240. This amount produced a moderate reaction at the site of injection, but no exacerbation of the dermatitis occurred. Thus treatment was maintained at this level, and the dermatoses of the hands disappeared within a short while.

*Summary.*—This was a case of bronchial asthma, which was clinically cured after two years of specific treatment, and did not recur. Two years later, the patient returned during the ragweed season, with a dermatitis. The localization on the elbows was brought under control by treatment with inhalant antigens. However, the affection of the hands was only cleared when injections of small amounts of trichophytin were added to the treatment.

Exacerbations have always the characteristics of a delayed reaction, in that they become apparent after twelve to seventy-two hours. They last three to five days. Some of the reactions described were annoying enough to require the use of antihistamines. However, they were never disturbing in the sense that signs of a systemic reaction became apparent. Moreover, they served as a useful guide in the search for the etiologic factors.

## 4

As will be seen from the preceding case reports, the dosage of antigen used for therapeutic purposes in this office and in the adult allergy clinic of the Bronx Hospital, and the pediatric allergy clinic of the Fordham Hospital, is at present much lower than was our practice in former years. This change, originating from both theoretical considerations and practical experience, has given us and others (Rowe,[5] Hansel,[3] Ratner,[4]) satisfactory results in the treatment of hay fever and bronchial asthma.

The occurrence of exacerbations of dermatitis with doses of pollen

antigens as low as 1 to 10 units and similarly with average doses of mold antigen taught us that these dermatoses are apt to be highly sensitive. By necessity, therefore, their treatment was started with very small quantities of antigen, for instance, one or a few tenths of a pollen unit. Subsequently, experience showed that these small doses are entirely sufficient for therapeutic results. This has already been brought out by the preceding case histories. And it is further emphasized by the therapeutic experience of Case 5, the account of which has been left incomplete in order to demonstrate the advantage of this type of procedure here.

*Case 5.*—C. W. (continued)—Treatment was continued on a perennial basis, and with each subsequent injection of only 4 pollen units of ragweed, the patient noted marked itching in the elbow areas. This was interpreted as an expression of overdosage. With the consent of the patient's mother, normal saline was injected without the patient's knowledge, to rule out a psychic factor. The patient reported no exacerbation. The dosage was therefore drastically lowered to 0.1 of a pollen unit of ragweed. All other pollens and dust were similarly lowered in dosage. From this moment on, improvement was striking and continuous. On June 26, 1951, about a year after treatment began, there was a temporary recurrence. The only area affected was the face and the back of the neck. Again on September 22, 1952, there was a mild eruption on the face, but the elbow and neck areas remained clear. It will be noted that both recurrences happened during the seasons of grass and ragweed pollination, with no relationship to food. The improvement has been maintained to date. The patient is now treated at fourteen-day intervals. Injections of house dust and ragweed are given at one time and the grasses, plantain, and tree (oak and birch) extracts at another visit, because any attempt to combine all the pollens into one treatment reproduces the atopic dermatitis, and causes renewed itching. The nasal and eye mucosae remain unchanged by overdosage affecting the skin.

*Summary.*—A case of allergic rhinitis and conjunctivitis with severe atopic dermatitis of long standing is described. Treatment with low doses of pollens and dust caused immediate improvement of the respiratory symptoms and clearing of the skin. However, 4 pollen units of ragweed was sufficient to cause itching at the cubital fossae. This reaction disappeared when the dose was reduced to 0.1 of a pollen unit without impairment of the therapeutic result.

It appears that the recommendation of low doses is equally true for house dust, pollens, and molds. Thus at present the treatment of cases of this kind is begun with doses as follows:

House dust 0.05 ml of 1:500 dilution.

All pollens 1/10 of a pollen unit.

Trichophytin 0.02 ml of a 1:120 or 1:240 dilution, intradermally.

Oidiomycin *(Monilia albicans)* 0.02 ml of a 1:200 or 1:300 dilution, intradermally.

If the results are satisfactory the dose for subsequent injections is not necessarily increased, or else if local reactions are absent, the dose may be increased by 10 per cent at two, three or four-day intervals to an upper limit of twice the starting dose. This refers mainly to house dust and pol-

lens. As far as molds are concerned, the dose is determined by the local reaction to the intradermal testing as well as the delayed reaction and systemic disturbance it produces.

It must be emphasized that the co-operation of the patients in reporting their progress, and their reactions to the treatment, is of great importance in determining the best course of procedure.

5

Under a regime of immunologic therapy as outlined in the preceding section, little additional therapy is needed. A minimum of local treatment is recommended. Calcium gluconate by mouth in large doses or parenterally was found helpful in reducing itching during the initial phase, but drugs known to cause allergic reactions such as barbiturates and bromides are avoided. Where infection complicates either the dermatosis or the concomitant respiratory allergy, every measure should be employed to remove this factor. Adequate treatment with an antibiotic given orally or intranasally (by means of aerosol) or by parenteral route appears to be particularly helpful in this respect.

## DISCUSSION

There was an incidence of 9.5 per cent of atopic dermatitis caused by the same antigen among our cases of respiratory allergy. Conversely, the presence of respiratory allergy in more than one-fourth of our cases of atopic dermatitis closely approaches the data recently reported by Rowe.[5] Both observations are in apparent contradiction with prevailing dermatologic opinion. In this respect it should be pointed out that there are obvious differences in the type of experience obtained in a general dermatologic practice or clinic as compared to that found in the office or clinic of an allergist. In the former case there is likely to be represented a random sample of the population which seeks dermatologic advice for a great variety of reasons. An allergist's experience with skin conditions is likely to develop around a restricted part of the population, namely, those with apparent or latent allergies. This may be an important factor in explaining the differences in the experience of allergists and dermatologists on the role of inhalants as causative agents in atopic dermatitis.

As our cases show (for instance, Case 2), the presence of an atopic dermatitis does not exclude allergic manifestations of different types such as contact dermatitis.

## SUMMARY

Among the 179 cases of respiratory allergy due to inhalants, atopic dermatitis was seen in twenty-three cases, or about 9.5 per cent of the total. Similarly, more than one out of four of the cases primarily seen for

atopic dermatitis had respiratory symptoms caused by inhalant antigens. Common etiologic agents were involved in both affections. Improvement of the dermatitis was observed when therapy with extracts from antigens involved in the respiratory allergy was started; also, temporary exacerbations of the dermatitis were observed within twelve to seventy-two hours after injections of overdoses of such extracts. Results were much better when therapeutic doses were employed much below those commonly used in the immunologic treatment of respiratory allergies of inhalant etiology.


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*1749 Grand Concourse*

ADDENDUM

Since this paper was submitted, Unger, L. A. and Unger, N. A. (ANNALS OF ALLERGY, Vol. 10, p. 574) reported that atopic dermatitis was found by them in not less than 106 out of 366 cases of bronchial asthma that they saw.

Furthermore, Tuft, L., and Hecht, M. V. (J. Allergy, Vol. 23, p. 528) also stressed the importance of inhalant allergens as causative agents for atopic dermatitis.

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## PENNSYLVANIA ALLERGY ASSOCIATION

The Pennsylvania Allergy Association will hold its spring meeting May 9 and 10, 1953, at the Bedford Springs Hotel, Bedford, Pennsylvania. An excellent program has been arranged, including round table discussions and a panel discussion on "Evaluation of Techniques and Therapy in Allergic Disorders." The annual banquet will be held at 7:00 P.M., Saturday, May 9.

Interns and residents of hospitals in the state of Pennsylvania are invited as guests of the Pennsylvania Allergy Association to attend scientific sessions.

# ACTH IN GELATIN

## Clinical Results With Repository Adrenocorticotropic Hormone in Allergic Diseases

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NUMEROUS reports in the literature in the last few years, since the ACTH clinical conference,[14] attest to the great value of both ACTH and cortisone in the production of remissions in the allergic diseases. Unlike cortisone, ACTH is inactive orally and must be given parenterally. The aqueous solution is conventionally given by the intramuscular route. Although patients can be safely treated in ambulatory fashion[1,2] by frequent intramuscular injections of the aqueous hormone, certain disadvantages are apparent by this method. (1) The treatment must be given initially at six, eight or twelve-hour intervals requiring frequent office or home visits unless self-administration is permitted. (2) A discontinuous stimulating effect on the adrenal cortex results. (3) Many patients develop severe local reactions characterized by pain, swelling and "lumps" when the hormone is given intramuscularly or subcutaneously. For these reasons the intravenous method was evolved. Gordon[5,6] based his introduction of the intravenous method on the observation that the adrenal cortex is in a state of constant activity and responds to minute doses of the hormone circulating in the blood. Other observations made during continuous ACTH intravenous drip showed that the adrenal cortex responds most effectively when mild stimulation is applied constantly, and by this means less hormone is used.[10]

Subsequently Hampton[7] confirmed that the clinical response, fasting eosinophil counts and 17-ketosteroid excretion studies all indicated a distinct advantage of ACTH given intravenously over the intramuscular route. The intravenous method however, is definitely a hospital procedure and requires constant supervision. Because of the obvious disadvantages to the use of aqueous ACTH by both the intramuscular and continuous intravenous methods, several attempts have been made to produce a sustained action vehicle for the intramuscular injection of the adrenocorticotropic hormone, which would simulate the effect of its administration by continuous intravenous drip. Peterman[13] recently reviewed the earlier attempts to produce a repository form of ACTH. The first such attempt[15] consisted in adsorbing the hormone onto colloidal aluminum-phosphate. This proved too irritating even when suspended in 18 per cent gelatin or when suspended in polyvinyl-pyrrolidone. Wolfson and his associates[16] subsequently introduced a more successful method which was developed

In part from the Allergy Clinic of the Children's Hospital of Michigan and the Wayne University, College of Medicine.

The ACTH in gelatin used is H.P. ACTHAR Gel® The Armour Laboratories, Chicago, Illinois.

by dissolving the hormone in propylene glycol before adding it to the colloidal aluminum-phosphate, which was suspended in the polyvinyl-pyrrolidone. No untoward reactions, except local irritation, occurred probably from the aluminum-phosphate. Later, Holbrook[9] used procaine in the same fashion as it is used in procaine penicillin adding 125 mg per cc as a solvent for the hormone. He was able to maintain his patients satisfactorily on one to two injections per day. More recently, Peterman[13] reported his results in twenty-four patients requiring ACTH therapy, using the daily allotment of hormone suspended in 18 per cent non-antigenic gelatin with 8 per cent dextrose added. Regardless of the daily amount of ACTH needed, the entire dosage was prepared by adding the hot sterile gelatin mixture to the vial containing the dry hormone and then adding sufficient of the vehicle in the syringe to make up 5 cc. He was careful not to inject the material too hot, or severe soreness resulted. It was necessary to keep the vehicle quite warm in order for it to maintain its fluid characteristics. His results showed that a maximum physiologic effect was achieved in from five to twelve hours. By means of circulating eosinophil counts, a high degree of physiologic activity was demonstrated to be sustained for eighteen to twenty-four hours, gradually becoming exhausted. His observations are in accord with those of many others, that the clinical response was not influenced by the type of eosinophil response. The so-called rebound symptoms, which often occur after single injections of the aqueous solution of the hormone did not appear. The sustaining action of the gelatin vehicle allowed the physiologic activity of the exogenous hormone to fade out slowly. By the constant sustaining physiologic activity of the hormone in gelatin, adequate clinical effect was maintained with approximately 60 per cent less hormone than by the more frequently required and more rapidly absorbed aqueous solution. In his series of twenty-four patients, excellent clinical response was noted with this method of repository hormone injection.

McCombs[11] used ACTH combined with purified gelatin, or suspended in sesame oil, and found that less hormone was required to produce the desired effect. His conclusion was that 40 units per day in a repository form, given in a single dose, seemed as effective as 60 to 80 units in divided doses when the aqueous hormone was used. He felt that the long-acting preparations of ACTH in gelatin gave the best results and required the smallest dosage. He reported on its use in five cases of chronic intractable asthma which required repeated courses of treatment. His observations are in agreement with those of many others in the treatment of chronic asthma, that is, that the intermittent use of ACTH aided in the avoidance of unpleasant side effects often associated with prolonged, continuous treatment.

In a more recent report Gay and Murgatroyd[4] used ACTH suspended in peanut or sesame oil in eight patients with contact dermatitis, with excellent results. Local reactions however, occurred using ACTH with these

vehicles. In an addendum to their report they stated that equally good results were later obtained with ACTH dissolved in gelatin. They made no mention of local reactions with the mixture of gelatin in use at that time.

The earlier commercial forms of ACTH in gelatin were prepared[12] by dissolving the hormone in 16 per cent pharmaceutical grade gelatin (derived from pork) along with 30 per cent propylene glycol and .5 per cent phenol. Recently the manufacturers have made available a preparation of highly purified ACTH in gelatin (H.P. ACTHAR Gel®) which consists of 16 per cent hydrolized gelatin from pork and .5 per cent phenol without propylene glycol.

We have recently had the opportunity of observing the clinical effects of this new repository form of ACTH in a group of thirty-seven allergic patients, both children and adults. We were particularly interested in the use of this material in the production of remissions in patients in severe allergic states, with ambulatory treatment. This report also includes three patients hospitalized for more severe conditions in which it was administered instead of the intramuscular or intravenous use of the aqueous form. We were also interested in observing the frequency and tendency to local reactions consisting of swelling, lumps, et cetera so often occurring with the use of the aqueous solutions of the hormone when administered intramuscularly.

*Patients Treated.*—This report is based on the use of this new form of ACTH in gelatin in thirty-seven patients in acute allergic states, twenty-six adults and eleven children divided as to allergic condition as follows:

| | Adults | Children |
|---|---|---|
| Severe asthma including status asthmaticus | 10 | 6 |
| Seasonal hay fever | 5 | 2 |
| Contact dermatitis | 3 | 1 |
| Chronic atopic eczema | 3 | 2 |
| Penicillin reactions | 4 | 0 |
| Drug reaction (Butazoladin®) | 1 | 0 |
| | 26 | 11 |

*Dosage.*—ACTH in gelatin is available in 5 cc multiple dose vials containing either 20 or 40 units per cc, and also in sterile lcc cartridges in similar potencies. This material is fluid at room temperature and is easily drawn through a 22 or 23-gauge needle, which we use in preference to larger gauge needles. The injections were administered intramuscularly either in the deltoids or glutei. Our adult patients were treated as follows:

First day, 40-60 units once or twice in twenty-four hours
Second day, 40-60 units once in twenty-four hours
Third day, 20-40 units once in twenty-four hours
Fourth day
Fifth day } 20 units if necessary once in twenty-four hours
Sixth day

TABLE I. DATA ON TWENTY-SIX ADULT PATIENTS TREATED WITH ACTH IN GELATIN INTRAMUSCULARLY

| No. | Pt. | Age | Sex | Diagnosis | Courses of Tmt. | Daily Dosage (units) ACTH Gel | Local Reactions or Side Effects | Results | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1 | T.S. | 60 | M | Status Asthmaticus 3 days | 1 | 60-60-40-40 | None | Excellent | Very severe pollen asthma; treated ambulatory, ordinarily would be hospitalized. (See detailed history). |
| 2 | S.Z. | 37 | M | Status Asthmaticus 2 days | 2 | 60-60-40-40-40<br>120-120-60-40-40 | None | Excellent | Treated ambulatory first course; several weeks later very severe relapse; hospitalized for second course. (See detailed history). |
| 3 | B.R. | 28 | F | Status Asthmaticus 3 days | 1 | 60-60-40-20 | None | Good | Very severe asthma with associated respiratory infection. Had almost complete freedom from asthma for two years, following specific treatment for several years previously. Oral cortisone while hospitalized had produced remission of very short duration one week before. |
| 4 | G.L. | 29 | F | Severe Asthma Several weeks | 1 | 60-60-40-20 | None | Excellent | Pollen and dust asthma with superimposed secondary infection; 600,000 units procaine penicillin G administered daily for three days. |
| 5 | R.P | 36 | M | Severe Asthma Perennial | 5 | 60-40<br>60-40-40<br>40-40-40-40<br>60-60-40-20<br>40-40 | None | Excellent each course | Very severe recurring asthma despite continuous anti-allergic measures Excellent response to each course of treatment with two to six weeks of freedom thereafter. |
| 6 | S.B. | 36 | F | Severe Asthma Perennial | 5 | 60-40-40<br>60-60-40<br>60-40-40-40<br>60-60-40-20<br>60-40-40-40-40 | None | Excellent each course | Very severe perennial asthma—definite bacterial sensitivity. Five hospitalizations in eighteen months prior to institution of ambulatory ACTH Gel—self administered. (See detailed history). |
| 7 | A.S. | 51 | M | Severe Asthma | 1 | 60-40-20 | None | Excellent | Grass pollen asthma, no previous specific treatment; no response to usual measures; dramatic relief twenty-four hours. |
| 8 | G.D. | 48 | M | Severe Asthma | 1 | 60-40-20-20 | None | Excellent | Fall pollen asthma with associated respiratory infection; no previous specific treatment; complete relief in forty-eight hours; procaine penicillin G, 600,000 units daily for three days. |
| 9 | D.S. | 36 | F | Severe Asthma | 1 | 60-40-20 | None | Excellent | Severe asthma followed sweeping out dusty, moldy basement; no response to several days ordinary anti-asthmatic treatment; rapid response and complete relief in forty-eight hours. |
| 10 | F.O. | 34 | F | Severe Asthma Aspirin | 1 | 60-60-40-20 | None | Excellent | Known aspirin-sensitive patient ingested 3.5 grains aspirin in error; developed severe asthma, almost anaphylactic in type. Required hospitalization. Rapid relief and complete freedom forty-eight hours after starting ACTH treatment. |
| 11 | L.L. | 52 | M | Weed Hay Fever | 1 | 60-40 | None | Excellent | Patient under treatment developed severe relapse September 5, 1952, due to excessive golf course exposure. Complete relief after second ACTH treatment Cortisone in previous years less effective for similar relapses. (See detailed history). |
| 12 | D.C. | 34 | F | Weed Hay Fever and Asthma | 1 | 40-40 | None | Excellent | Previous seasons mild; no specific treatment. September 1952, severe hay fever and asthma one week; dramatic relief in twenty-four hours. |
| 13 | L.M. | 27 | M | Grass Hay Fever and Asthma | 1 | 40-40 | None | Excellent | Hay fever and asthma first time June 1952. Complete relief in forty-eight hours. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 14 | C.F. | 18 | M | Grass Hay Fever | 1 | 40-20 | None | Excellent | Mild grass hay fever several years; no treatment required. Developed severe hay fever 1952, season. Good relief in twenty-four hours. |
| 15 | G.T. | 17 | F | Weed Hay Fever | 1 | 40-20 | None | Excellent | Severe hay fever several years; good results with specific treatment; no treatment for three years. Mild hay fever August 1952, with very severe relapse September 1952. Good relief in twenty-four hours. |
| 16 | J.D. | 36 | M | Penicillin Reaction | 1 | 120-80-40-20 | None | Excellent | Severe urticaria and angio-edema several weeks duration. Several penicillin injections ending eighteen days previously. Poor response to Cortisone orally 200 mg daily for three days; dramatic response to ACTH Gel. No recurrence. |
| 17 | O.L. | 27 | M | Penicillin Reaction | 1 | 120-120-60-40-30 | None | Excellent | Severe urticaria and angio-edema for three weeks after single penicillin injection. No relief from usual measures. Completely free of symptoms in three days. No recurrence. |
| 18 | P.J. | 51 | F | Penicillin Reaction | 1 | 120-80-40-20 | None | Excellent | Severe pruritis and urticaria two days after last of several penicillin injections. No response to three days treatment with oral Cortisone. Dosage ? Complete relief after four days. No recurrence. |
| 19 | G.O. | 26 | M | Penicillin Reaction | 1 | 80-40-40-40 | None | Excellent | Severe angio-edema and urticaria two weeks after last of several penicillin injections. Moderate response to oral Cortisone 100 mg daily for three days. Dramatic clearing after three days of ACTH in gelatin. No recurrence. |
| 20 | P.M. | 24 | M | Drug Reaction (Butazolidin) | 1 | 120-120-60-60 | None | Excellent | Was hospitalized because of severe urticaria and angio-edema two months duration. Butazolidin R treatment for arthritis. Slight improvement with oral cortisone. Complete clearing by third day with ACTH. No relapse. |
| 21 | A.K. | 28 | M | Chronic Atopic Eczema | 1 | 60-60-40 | None | Marked Improvement | Patient chiefly sensitive to house dust; had discontinued treatment. Several relapses since onset of cold weather. Marked improvement followed first injection of ACTH Gel. Small intradermal injections 1-10,000 dust maintained his improvement. |
| 22 | L.M. | 19 | F | Chronic Atopic Eczema | 1 | 60-40-20 | None | Marked Improvement | Eczema all her life despite much local and general treatment. No allergic studies. ACTH produced dramatic relief and enabled skin testing to be carried out subsequently. |
| 23 | M.B. | 32 | F | Chronic Atopic Eczema | 2 | 60-60-40-40<br>120-60-40-40 | None<br>None | Marked Improvement | Severe chronic eczema all her life. Many foods and inhalants implicated. ACTH gave rapid and remarkable relief for two severe relapses while undergoing allergic studies and treatment. |
| 24 | L.A. | 28 | M | Contact Dermatitis | 1 | 60-60-40-0-40-20-0<br>20-20-20-0-20<br>20-0-20 | None | Marked Improvement | Photographic lab worker, developed very intense contact dermatitis from Potassium Dichromate. No improvement after two weeks orthodox treatment. |
| 25 | B.B. | 47 | F | Contact Dermatitis | 1 | 60-60-40-40-40-20 | None | Marked Improvement | Severe dermatitis several years duration with many relapses due to pyrethrum in insect sprays. |
| 26 | C.F. | 33 | F | Contact Dermatitis | 1 | 60-60-40-20 | None | Marked Improvement | Severe dermatitis in florist from chrysanthemum. |

TABLE II. DATA ON ELEVEN CHILDREN TREATED WITH ACTH IN GELATIN INTRAMUSCULARLY

| No. | Pt. | Age | Sex | Diagnosis | Courses of Tmt. | Daily Dosage (units) ACTH Gel | Local Reactions or Side Effects | Results | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M.W. | 2 | M | Asthma | 3 | 20<br>20<br>20 | None<br>None<br>None | Marked Relief<br>Marked Relief<br>Marked Relief | Perennial asthma since age eight months. Greatly improved on specific desensitization treatment. Marked relief and shortening of severe attacks with single doses of ACTH Gel at intervals of one to three months. |
| 2 | P.W. | 5 | M | Asthma | 20 | 20<br>1-2 days each course | None | Excellent | Severe perennial asthma three years. No results from many types of treatment including complete allergic studies. Psychological treatment of child and family for several months—no improvement; 20 units ACTH Gel once or twice at two to six week intervals keeps this child completely free of asthma. (See detailed history). |
| 3 | A.L. | 8 | M | Status Asthmaticus | 1 | 20-20-10 | None | Marked Improvement | Severe perennial asthma under specific treatment. Status asthmaticus followed respiratory infection. ACTH Gel prevented hospitalization. |
| 4 | J.P. | 9 | F | Pollen Asthma | 1 | 40-20 | None | Marked Improvement | Mild hay fever fall 1951; severe hay fever with asthma September 1952. No previous specific treatment. Marked relief in twenty-four hours. Co-seasonal pollen treatment successful for remainder of season. |
| 5 | D.C. | 4 | M | Pollen Asthma | 1 | 20-10 | None | Marked Relief | Slight hay fever fall 1950 and 1951; severe asthma developed suddenly September 1952. Marked relief after second injection of ACTH Gel. Co-seasonal pollen treatment sufficient for remainder of season. |
| 6 | E.D. | 5 | F | Pollen Asthma | 1 | 20 | None | Marked Improvement | Patient under treatment for weed pollen hay fever and asthma. Developed severe asthma at height of season in Spetember 1952. Complete relief followed single injection of ACTH Gel. Remainder of season good results with specific treatment. |
| 7 | K.S. | 9 | M | Hay Fever | 1 | 40-40 | None | Marked Improvement | Patient had previously had severe fall pollen hay fever and asthma. During September 1952 while undergoing specific pollen treatment had severe hay fever but no asthma during first week of September. Two injections of ACTH Gel on successive days produced marked improvement. Hyposensitization treatment was continued. |
| 8 | G.T. | 5 | F | Hay Fever | 1 | 20 | None | Marked Improvement | Severe pollen hay fever for first time in September 1952. Single injection of ACTH was followed by marked improvement. Patient continued comfortable on co-seasonal pollen treatment. |
| 9 | J.M. | 10 | F | Chronic Atopic Eczema | 1 | 40-20 | None | Good | Chronic eczema all her life. ACTH when first seen produced marked relief. Allergic studies and treatment were then begun. |
| 10 | D.J. | 10 | F | Chronic Atopic Eczema | 1 | 40-40-20 | None | Good | Severe chronic eczema. Marked relief after ACTH sufficient to start skin testing and allergic management. |
| 11 | S.C. | 8 | M | Contact Dermatitis (Poison Ivy) | 1 | 40-20-20 | None | Good | Severe poison ivy; history of occurrence each year generally lasting for weeks. Marked improvement after second injection of ACTH Gel. Duration of illness appreciably shortened, as compared to previous attacks. |

Patients were rarely treated longer than three to five days. Children received proportionately less, usually 20 units once the first day followed by 10 to 20 units daily for subsequent injections if necessary for several additional days.

*Local Reactions.*—One of the serious disadvantages, besides the necessity of frequent administration in the use of the aqueous preparation intramuscularly is the tendency to severe local reactions which occur in many patients. It is noteworthy that with the use of this new repository form of the hormone not a single local reaction of any consequence occurred in approximately 180 injections in this series of thirty-seven patients. The injections were for the most part entirely painless. Several patients received repeated courses of ACTH in gelatin without the development of local discomfort or other evidence of a sensitivity reaction.

*Side Reactions.*—No undesirable physiologic effects were seen in this group of patients. It is well known that such undesirable side reactions occur usually after prolonged treatment. For this reason it is our practice to limit the use of ACTH or cortisone to short courses of treatment sufficient to produce a remission during an acute allergic state. We discontinue the use of either cortisone or ACTH as quickly as possible after improvement occurs, usually at the end of the third to the fifth day of treatment. With improvement in the patients condition, orthodox forms of anti-allergic treatment should be instituted. By keeping the period of the administration of these powerful hormones to the minimum period of time, side reactions are avoided.

*Laboratory and Patient Supervision.*—As pointed out by Brown[2] studies of circulating eosinophiles and 17-ketosteroids in patients undergoing short periods of treatment for allergic diseases are not necessarily correllated to dosage, are costly to the patient and unnecessary to good clinical management. Such studies were not carried out in these patients receiving short courses of treatment. There is a wealth of experimental data in the files of the manufacturer[12] indicating that the ACTH effect on circulating eosinophiles and 17-ketosteroids are the same with this hormone in repository form as with the aqueous solutions, with the exception of its retardant and more prolonged effect with smaller doses. Careful supervision of the patient however is advisable from the standpoint of blood pressure and urinary sugar, even during short courses of therapy with the adrenocorticotropic hormone.

*Results.*—The therapeutic response to the intramuscular or subcutaneous injection of ACTH in gelatin was good to excellent in all thirty-seven patients both children and adults. None of the patients in this series failed to show definite clinical improvement with the use of the adrenocorticotropic

hormone in repository form. All patients were treated on an ambulatory basis except adult Cases 2, 10 and 20, who were hospitalized. Many of the other patients were ill enough to have been hospitalized for conventional ACTH therapy with the aqueous solution had not the repository form been available. The details of treatment of several patients follows: All the patients treated are summarized in Tables I and II.

*Asthma.*—The following case reports exemplify our use of ACTH Gel in cases of severe asthma.

*Case 1.*—(Table I) T. S., a man, aged sixty, had had fall hay fever and asthma for many years. He had been treated previously in many clinics. His treatment had been, for the most part, intermittent and generally symptomatic, because of poor cooperation. He was seen first during the early part of September 1952, in very severe asthma. After a few days of symptomatic treatment, during which time he became worse and developed status asthmaticus, it was decided to hospitalize him. He resisted this suggestion. Ambulatory treatment with ACTH in gelatin was instituted. He was given 60 units the first day and noticed definite relief that evening. The following day he was markedly improved and was given another 60 units. On the third and fourth days he was given 40 units after which no ACTH was used. He was then almost completely free of symptoms. Treatment with small intradermal injections of ragweed pollen was instituted daily, then every other day. He was able to carry on during the remainder of the ragweed pollen season with only occasional mild difficulty.

*Case 2.*—(Table I) A man, aged thirty-eight had been deserted by his wife four years previously, and left with four children varying in age from two to eight years. It was necessary because of economic conditions for him to assume the burden of the household duties as well as to continue working in an industrial plant in order to gain a livelihood. He developed asthma two years later. During the past six months his asthma had become very severe, almost incapacitating. He had had considerable symptomatic treatment previously, including intravenous aminophyllin, repository epinephrine injections and many types of antihistaminic and sympathomimetic drugs. When first seen he was in status asthmaticus, and under ordinary circumstances would have been hospitalized for treatment. Because of his difficult domestic situation and his inability to obtain care for his children, it was decided to treat him on an ambulatory basis with ACTH in gelatin. He was given 60 units intramuscularly on two successive days and 40 units intramuscularly on the third, fourth and fifth days. At the end of that time, his improvement was such that complete allergic studies could be carried out by means of both scratch and intradermal skin testing. He was found to be very sensitive to house dust and to the industrial dust to which he was exposed at his place of employment. Dust precautions and hyposensitization with small doses of the implicated dusts continued his excellent improvement. Several weeks later, he developed a severe respiratory infection and again status asthmaticus. He was now able to obtain domestic help so that he could be hospitalized. Treatment with ACTH in gelatin was instituted as follows: 60 units on the first, second and third day and 40 units on the fourth and fifth days after which the hormone was discontinued. At the same time procaine penicillin G was injected intramuscularly, 300,000 units twice a day. His symptoms were completely relieved by the fifth day. At the time of this report he has remained almost entirely free of symptoms, a period of over three months. During this time, immunization with small doses of the implicated dusts have been continued.

*Case 6.*—(Table I) S.B., a thirty-six-year-old woman, developed severe asthma following a bronchial infection in the spring of 1950. Severe attacks of asthma recurred every six to eight weeks thereafter initiated by respiratory infections and accompanied by purulent sputum. Complete allergic studies by means of both scratch and intradermal tests gave almost completely negative results. With each respiratory infection she usually developed status asthmaticus and required hospitalization. She was admitted to various hospitals five times in eighteen months. She was re-studied in three different institutions during this period of time with negative findings, except for the presence of a respiratory infection with each attack. She developed unusual reactions to all antibiotics tried except penicillin which was given parenterally in doses of 600,000 units for seven to ten days during each attack. She was definitely sensitive to many drugs including the barbiturates, opium derivatives, sulfa drugs and most antibiotics except penicillin. A skin test with an autogenous vaccine gave a four plus delayed skin reaction and produced a very severe relapse requiring hospitalization.

Cortisone was ineffective during her periods of severe asthma. She responded to ACTH in aqueous solution intramuscularly, but developed severe local reactions to each injection. Intravenous ACTH on one admission was very effective.

She has been taught self-administration of ACTH in gelatin and during the past year she has administered to herself five courses of treatment. The attacks are usually brought under rapid control with from three to five daily injections of 40 to 60 units. Between attacks she has been taught to administer .05 cc of 1:1000 autogenous vaccine every day intradermally in an effort to overcome the apparent bacterial sensitivity.

Strong psychosomatic factors were present in this case. The patient was very obese. This may have been the result of, or one of the causes of, a very trying marital situation, the details of which are not pertinent to this report. It has been possible during the past year to overcome each of her relapses within three to five days without hospitalization despite the impossibility of altering the serious psychologic difficulties in this patient's personal life.

*Case 3.*—(Table II) P.W.*, aged five years has had very severe asthma since six months of age. Complete allergic studies did not reveal the cause of his difficulties. Severe asthmatic attacks occurred almost daily and he had been hospitalized for status asthmaticus on numerous occasions. A skin test with an autogenous vaccine made from cultures from his nose and throat gave a two plus delayed skin reaction. Subsequent immunization with weak dilutions of this vaccine were ineffective in preventing attacks perhaps because treatment was not persistent.

A strong psychosomatic element was suspected. Several months of study and treatment by a clinical psychologist did not seem to improve the situation. During one of his severe attacks, his pediatrician administered 20 units of ACTH in gelatin. Within a few hours the patient was completely relieved and the child remained free of symptoms for three weeks. Subsequently whenever he developed severe wheezing, 20 units of ACTH in gelatin was administered with the same excellent response. He has averaged one to two injections of 20 units every two to six weeks during the past eighteen months. Each course has been followed by dramatic relief of several weeks duration. Apparently no undesirable physiologic effects have occurred during this period of time. Previous use of cortisone orally in the same circumstances was much less effective in producing remissions.

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*Courtesy Dr. Irving Burton.

*Hay Fever.*—Several cases of severe hay fever some accompanied by asthma have been treated with ACTH in gelatin during the 1952 pollen season with excellent results. The following cases are illustrative:

*Case 11.*—(Table I) L. L., aged fifty, had been under treatment for fall hay fever for several years with satisfactory results. During the first week of September 1952, following the same dosage schedule of pollen extract which was previously used with considerable success, he developed violent hay fever symptoms of the eyes and nose and some wheezing. The patient suspected that his symptoms had been aggravated by long sessions on the golf course on two successive day. He was given 40 units ACTH in gelatin on two successive days with almost complete relief of his asthma and hay fever symptoms. Treatment with his pollen extract was continued with the same dosage as before with no further relapse during the season.

*Case 5.*—(Table II) D.C., aged four years, was first seen during the height of the ragweed season in the fall of 1952. He had had mild hay fever during the two previous ragweed seasons which had responded quite well to symptomatic measures. During the first week of September 1952, his symptoms became markedly aggravated, severe cough and moderate wheezing developed. Scratch tests for the fall pollens revealed strong sensitivity to the weeds. Local therapy for his nasal and ocular symptoms were relatively ineffective as was other symptomatic treatment directed towards controlling his cough and asthma. He was given 20 units then 10 units ACTH in gelatin on two successive days, following which his symptoms were alleviated almost completely. He was carried through the remainder of the ragweed season with small injections of the weed pollens intradermally, two to three times weekly, without further relapse.

*Chronic Atopic Eczema.*—The use of ACTH or cortisone is inadvisable in chronic allergic conditions except for short courses of treatment for the production of remissions during acute relapses. Undesirable physiologic effects which may occur following the prolonged usage of either of these hormones can be avoided by limiting the use of these substances to short periods of time sufficient to enable the allergist to institute allergic studies and subsequent specific and appropriate symptomatic treatment.

*Case 22.*—(Table I) L. M., a girl, aged nineteen, has had chronic atopic eczema all her life. The condition was much worse during parts of the summer and in the height of the winter. Early in life the flexural areas and back of the neck only had been affected. In recent years the dermatitis had extended so that when first seen in the fall of 1952, the entire skin area other than the lower portions of the legs was involved. The face was swollen and itchy and there were numerous excoriated and weeping areas in various parts of the body. She had had a great variety of local and symptomatic treatment during her long illness with only temporary benefit. Treatment with ACTH in gelatin was instituted as follows: 60-40-20 units on three successive days. She experienced very remarkable relief of her itching within twenty-four hours. Appropriate local treatment was begun. The dermatitis improved considerably and at the end of two weeks sufficient healed skin surface was available for carrying out both scratch and intradermal skin tests. These revealed positive skin reactions to many common foods, most of the pollens of the tree, grass and weed seasons, several dusts and most of the molds that were tested. Subsequent clinical trial revealed that milk and orange were the only implicated foods and that

her chief sensitivities were to the inhalants. The first injection of autogenous house dust 1:1000 produced a severe relapse. The material was then restarted at 1:100,000 dilution, .05 cc intradermally, with gradual improvement in her condition. She is presently under treatment with dusts, pollens and molds, with considerable improvement.

*Concomitant Treatment.*—It is well recognized that in themselves ACTH and cortisone do not produce cures in the allergic diseases, but enable other forms of conventional therapy to become effective. It is particularly important that treatment directed toward the etiologic factors should be carried out. This is especially true of the necessity for the elimination of inhalant and ingested allergens and contactants. The associated use of antibiotics for superimposed infections both respiratory and dermal is important. It is our practice to use either procaine penicillin G parenterally or terramycin and aureomycin orally when indicated, in adequate dosage. Appropriate local treatment for eczema and other forms of the allergic dermatoses should be carried out. The details of such treatment can be found in numerous publications and need not be given in detail here.

## DISCUSSION

It is obvious that ACTH in gelatin produces a sustained hormonal effect with as few as one injection daily in most cases. We have noticed that there was no need in our series of patients for "tapering-off" the dosage with repository treatment as would be necessary using the aqueous solution. The reason for this perhaps is that the stimulating effect of the hormone when given in gelatin gradually diminishes and an automatic tapering-off effect results. It is interesting to note that the results in the severely ill patients including three that were hospitalized were as dramatic with the sustained acting hormone as that which we have observed in other instances when the aqueous hormone was given intramuscularly at frequent intervals, or by continuous intravenous drip. We are inclined to agree with Hansel[8] that the gelatin preparation may replace to a great extent the other methods of administering ACTH. Even in hospitalized cases this may be the method of choice. The possible dangers and technical difficulties inherent in the continuous intravenous drip method can be thus avoided. The same precautions and contraindications in regard to the administration of ACTH in gelatin exists as for the aqueous solution. These contraindications to its use have been discussed fully in the literature and do not require elaboration in this report.

It should be emphasized that the etiologic diagnosis in the allergic diseases is just as important today as it was before the development of ACTH and cortisone treatment. Cooke[3] states that he has never seen long lasting results from such treatment unless the responsible agent or allergen is removed or treated—"potent and spectacular as the results may be, they are purely symptomatic and temporary."

SUMMARY

1. Twenty-six adults and eleven children in various acute allergic states were treated with a new preparation of ACTH in gelatin (H.P. ACTHAR GEL®). Good to excellent clinical results were observed in all cases.

2. All patients in this series were treated on an ambulatory basis with the exception of three who were hospitalized.

3. Good results were obtained in most cases with single injections per day of 40 to 60 units for two to five days. Children were given proportionately lower doses of from ten to twenty units per day.

4. Injections of ACTH in gelatin are almost completely painless. No local or general reactions occurred. No undesirable side effects were seen.

5. No evidence of allergic sensitivity to the material was observed in several patients requiring repeated courses of treatment.

6. Ambulatory treatment with this preparation in patients in acute allergic states is possible in many of those who would otherwise require hospitalization.

7. The need for continuous intravenous drip with the aqueous solution of ACTH should be rarely necessary because of the similar continuous mild stimulation resulting from the use of the repository form of ACTH.

8. The need for appropriate concomitant symptomatic treatment including the use of antibiotics when indicated is stressed.

9. The use of ACTH in gelatin does not obviate the need for careful and thorough allergic study and treatment.

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*469 Fisher Bldg.*

## EUROPEAN MEETINGS

Those members of the College who contemplate a trip to Europe this spring should arrange their schedule so as to attend the round table discussions and scientific program of the Dutch Allergy Society to be held at Utrecht and Groningen, May 14 to May 16, 1953. Elaborate arrangements have been made for entertainment, visiting The Hague, pharmaceutical houses, a trip to Doorn and the tulip bulb and flower exposition, for which Holland is noted. This time of the year is particularly beautiful in Northern Europe, and distances are very short.

On May 20 to 23, 1953, the Second European Congress of Allergology will be held at Copenhagen, Denmark, under the auspices of the International Association of Allergologists. Outstanding scientists of Europe will participate in the program. Those planning to attend the Holland sessions are requested to write Dr. Quarles van Ufford, Secretary, Ennakaan 17, Utrecht. For information on the Second European Congress to be held at Copenhagen, write to Dr. Egon Bruun, Secretary General, 8 Gersonsvej, Hellerup, Copenhagen, Denmark.

# PERSISTENCE OF HISTAMINIC RESPONSES IN THE HUMAN DURING CHOLINESTERASE ADMINISTRATION

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THE ROLE of the acetylcholine (ACh) splitting enzyme, cholinesterase (ChE), in a non-effector organ such as blood, has been subjected to some debate. Classic theory made no allowance for its presence there until the work of Greig and her collaborators[9] indicated that the ACh-ChE mechanism, along with the synthesizing enzyme, choline-acetylase, might compose a ubiquitous cellular system regulating permeability to cations.[10] The last hypothesis furnished an explanation for that portion of the blood "transport" ChE found in the erythrocyte but left unexplained the presence of a distinguishable "pseudocholinesterase" in the noncellular portion, the plasma. It has been tacitly assumed that the plasma ChE, though possessing a strong valency for ACh, was either concerned in the function of other esters or else was merely an accidental incursant into plasma's composition.

This last assumption, however, has not had universal acceptance. It has been pointed out, for instance, that in the human ACh systemic "flooding" by seepage from overactive thalamic and hypothalamic grey matter, may be a physiologic or pathologic event.[2]

Non-cellular or "transport" cholinesterases could conceivably function to limit the effects of ACh seepage. The point could not be tested until the blood cholinesterase could be substitutively raised without introduction of artifact as would be the case in plasma or whole blood infusion.

Relatively pure human ChE preparations, whose injection will raise the ChE content of blood and tissues, have become available. Substitutive plasma ChE rise thus produced has been attended by certain pharmacologic and therapeutic effects; among these is one by which certain hypersensitivity or allergic phenomena have been abrogated.[4] The latter effect has been compared to the "glucocorticoid" effect of the eleven oxysteroids,[5] but similar effects might emerge if ChE had antihistamine effects instead. While Rentz[11] has reported histamine to antagonize cholinesterase, our own observations show no effect for ChE administration on histamine responses *in vivo*.

## EXPERIMENTAL

Both human subjects and animals (cats and guinea pigs) were used for elicitation of histaminic effects. In humans, these consisted in the production of histamine wheals and in the acidity titration of the fractional gastric test meal. In animals, the depressor response to his-

From the Research Division, Rystan Company, Inc., Mount Vernon, New York.

tamine (cats) and the skin wheal diameter produced by histamine (guinea pigs) was measured. Both of these experimental animals have, normally, a very low blood ChE. In the experimental instances the latter was raised, as it was in human subjects by the preadministration of purified human plasma ChE* solution. Human subjects were in one of two categories: (1) those with untreated acute leukemia in which the blood ChE is markedly depressed, and (2) those with antihistamine resistant atopic dermatoses, in which the blood ChE is usually at the upper level of normal.

In all subjects, both animal and human, the administration of ChE was made intravenously and the resulting blood ChE level was calculated from the injected unitage on a quantitative basis, the propriety of such calculation having been established in a previous investigation;[6] occasionally the extent of this rise was directly determined in a human subject by the method of Alles and Hawes.[1]

In two instances, in cat experiments, beef erythrocyte cholinesterase** was used in place of the human plasma ChE (with exactly comparable negative results) to counter the contention, certain to be advanced, that plasma ChE is a "pseudo" esterase. This forensic argument, wholly inapplicable in any event since the purpose of the administrations was to raise the blood ChE and neutralize the pharmacologic activity of ACh (and any enzyme which hydrolyzes ACh is, by definition, a cholinesterase) is answered by the fact that what purports to be a "true" esterase, beef erythrocyte ChE does not differ in this *in vivo* respect from plasma ChE.

## RESULTS

In four human leukemic subjects, neither the size of a histamine wheal induced on the skin of the extensor surface of the forearm by intradermal injection of 0.05 cc of a 1:10,000 solution of histamine diphosphate, nor the duration of the wheal was significantly different either before or after the administration, intravenously, of 12,000 Alles and Hawes units of human plasma ChE (comparable in ChE content to 6 liters of human plasma). Similar absence of any effect on the size or persistence of the histamine wheal was evinced by four subjects with atopic dermatosis whose initial blood ChE levels were normal and whose blood ChE levels were kept artificially doubled over a seventy-two-hour period by the repeated intravenous administrations of ChE.

In four human subjects without atopic disease, the highest dilution of aqeous histamine diphosphate which would give a perceptible "flare" on the skin of the forearm was determined. Serial dilutions of the histamine

*Provided by Dr. Fred F. Johnson of the Cutter Laboratories, Berkeley, California. This consisted in IV-6-1, IV-6-3 and IV-6-4 subfractions, some of which were 1,500 times whole human plasma in ChE content. In later experiments, "Cholase-Cutter" with ChE content of about .5 liter of human plasma/cc. was used.

**Obtained through the courtesy of Dr. Melvin Thompson of Winthrop-Stearns, Inc., New York City.

salt, in aqueous plasma ChE having a unitage of 1000/ml was then made and the highest dilution of this mixture compared for "flare" potency with the plain aqueous histamine. Here again there was no signficance in the absolute amount of histamine necessary to produce a perceptible "flare" (about 0.4 microgram in each instance) in the presence or absence of plasma ChE.

A histamine-impelled gastric acidity titration showed no significant difference in a patient with non-Addisonian megaloblastic anemia before and after the administration of sufficient human plasma ChE to raise the blood level of the enzyme to over 20 per cent above its preadministration level (Table I). An even higher percentage rise was ineffective.

With one exception, no adverse effects were noticed after plasma ChE infusion in the human subjects. In this single instance, the administration of 18,000 units in a five-minute period was followed by mild disorientation and enhanced psychomotor activity lasting for about four hours after the administration. While this occurrence may have been coincidental, doses of this magnitude have not been repeated in humans. In the four subjects with atopic dermatoses, all of which had been antihistamine resistant, there was such rapid and complete clearing of all skin lesions (within twenty-four to forty-eight hours in each instance) that the effect could not be considered coincidental. It has now been duplicated in cases of pemphigus vulgaris, lupus erythematosis, leukemia cutis and erythema multiforme. This finding, though not germane to the present study, may nevertheless be cited to counter the point that failure to abrogate histaminic effects, therein was not due to pharmacodynamic inertia of the test material.

In cats, the vasodepressor effect of histamine was not abolished by Cholase administration though in one instance of hypotensive shock developing in this animal during the course of protracted anesthesia, the demonstrated analeptic effect of Cholase was quite dramatic and sustained. Hypotensive shock accompanying myocardial infarction in a human was successfully combatted by plasma ChE infusion.

Since water-soluble chlorophyllins of the Chloresium type (potassium cupri chlorophyllinate) have sporadically been reported to possess topical "antiallergic" effects and to potentiate the action of such antihistamines and sympathomimetics as desoxyephedrine, a series of *in vitro* experiments with Chloresium over a wide range of concentrations (from 0.01 to .5 per cent) were undertaken. The results of these may be summarized by the statement that it was inert against the ACh-ChE system of erythrocytes, plasma or their composite (as in whole citrated blood). It neither potentiated nor depressed the activity of the enzymes in these environments nor did it remove nor enhance the anti-esterase activity of esserine. One possibility that chlorophyllins might augment ChE activity after systemic administration through its reputed hemopoietic activity (the source of erythrocyte ChE being the hemopoietic marrow) is under present investigation.

TABLE I. FAILURE OF CHOLASE INFUSION TO MODIFY HISTAMINE-IMPELLED CHLORHYDRIA

Subject: A. F., Acquired Hemolytic Anemia (with megaloblastic marrow)

| Date | 11-7-51 | | 11-11-51 | | 11-21-51 | |
|---|---|---|---|---|---|---|
| Blood ChE | 3.63 | | 4.41* | | 4.02 | |
| Time | Free HCl | Total | Free HCl | Total | Free HCl | Total† |
| 0** | 0 | 6 | 1 | 8 | 2 | 10 |
| 15 min. | 14 | 30 | 9 | 14 | 22 | 29 |
| 30 min. | 12 | 36 | 16 | 28 | 24 | 41 |
| 45 min. | 21 | 39 | 25 | 36 | 22 | 43 |
| 60 min. | 17 | 33 | 22 | 35 | 18 | 38 |
| 90 min. | 7 | 19 | 18 | 28 | 18 | 33 |

*48 hours after single intravenous administration of 2500 Alles and Hawes units ChE

Subject: M. J., Gastric Carcinoma

| Date | 9-3-52 | | 9-6-52 | |
|---|---|---|---|---|
| Blood ChE | 3.07 | | 4.67* | |
| Time | Free HCl | Total | Free HCl | Total*** |
| 0** | 4 | 9 | 0 | 4 |
| 30 min. | 32 | 47 | 28 | 43 |
| 60 min. | 29 | 45 | 24 | 44 |
| 90 min. | 6 | 18 | 11 | 21 |

*72 hours following single intravenous administration of 5000 Alles and Hawes units ChE
**0.01 mgm histamine per kilogram given subcutaneously
†As "clinical units" determined on 5cc withdrawal specimen.

## DISCUSSION

The histamine theory as it relates to hypersensitivity states (allergy, atopy and anaphylaxis) has received tremendous impetus from the advent of "antihistamines" or substances so designated which were believed to act as specific blocking agents at the histamine-effector organ. The popularity of this theory may be disproportionate to the amount of supporting fact. Antihistamines, while invariably effective in submerging hypersensitivity in the guinea pig, are totally ineffective in this same connection in the mouse; in the human, though authorities differ in the degree of hypersensitivity alleviation, they nevertheless agree that antihistamines are not universally effective. Definitive adrenocorticotherapeutic agents (ACE, ACTH and 11-oxysteroids) and indirect adrenocorticomimetics (mycin antibiotics, water-soluble chlorophyllins) will abolish certain hypersensitivity phenomena in humans whereas none of these will counteract histamine shock in the guinea pig. Sexton[12] has recently adduced evidence for a theory which dissociates conclusions drawn from those classically ascribed—that in addition to blocking a histamine responsive effector organ, antihistamines may also limit systemic ACh production by a direct depression of the thalamus while at the same time, by diminishing intestinal wall permeability, they limit absorption of intestinally derived cholinergics. The implications of this interesting theory must be considered in light of further investigation.

That ACh, or some other ChE substrate, and not histamine, may be

the invidious antigen-antibody reaction product concerned in human hypersensitivity phenomena, has repeatedly been suggested. Protein degradation products of the proteose class ("peptones") have repeatedly been incriminated in this connection. It is of interest that ChE infusion vitiates peptone shock in cats[4] and that Hanke and Koessler[8] were able to prepare an extremely toxic "peptone" free from histamine. Demonstration of non-intervention with histamine effects by ChE may be a necessary prelude to the ascertainment of the role of this enzyme in the abrogation of shock and hypersensitivity states.

## SUMMARY AND CONCLUSIONS

No interference with the effects of histamine administration to humans was shown by concurrent cholinesterase administration. This negative result was corroborated by restricted experiments on cats and guinea pigs. Some implication of this inertia in connection with the histamine versus acetylcholine theories of hypersensitivity state is indicated.

## ACKNOWLEDGMENTS

Valuable technical guidance and assistance in the animal studies was afforded by Drs. S. Y. P'an and Elliott R. Weyer of Chas. Pfizer & Co., Brooklyn, New York. Human subjects in whom cholinesterase infusion was justified as a therapeutic measure were assigned by Drs. David Kershmer and Leon N. Kessler of the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn. In each instance, these physicians exercised supervisory clinical care. Dr. Edward Sexton has graciously given permission for citation of his unpublished data on certain antihistamines.

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# A WHOLE POLLEN ANTIGEN HYDROCHLORIDE

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THE PREVENTION and treatment of hay fever by the injection of crude pollen extract in gradually increasing doses, as introduced by Noon in 1911,[10] is clinically effective. This method, however, requires many injections and is fraught with the constant danger of systemic reactions. To prevent these reactions, clinicians have tried alum-precipitated pollen antigen,[2,4,5,18] pollen antigen emulsions in oil,[6,8,20] pollen antigen in gelatin,[3,6] pollen antigen precipitated as the tannate,[14] pollen hydrochloride,[11,12] and more recently crude pollen extract in combination with one of the antihistamines.[7,17]

None of the above modifications have proved satisfactory except the hydrochloride and possibly the mixtures with antihistamines. The antihistamines used, which are hydrochlorides, tartrates, or maleates, form an acid salt with the pollen antigen. Their delayed effect is due in part at least to an action similar to, or the same as, pollen antigen hydrochloride.

All preparations of pollen antigen have been the crude extract or purification products of the crude extract. This has been necessary because the fragility of the pollen antigen permitted sterilization only by filtration such as Seitz filtration. The acid salts, however, are more stable.

Most investigators have concluded that there are two or more active fractions in crude pollen extracts.[9,19] We were able to isolate five fractions;[13] and Abramson,[1] six or more fractions. There is nothing to indicate, however, that all of the fractions dissolve out in the extract. After extraction the residual pollen will still produce a positive skin reaction in a sensitive patient. Further, the fractions most easily extracted are those with low molecular weight, which gives a maximum amount of constitutional reaction with a minimum amount of desensitization. It has been found by repeated extraction and the determination of antigen in the residual pollen that only one-sixth of the active antigen is extracted by the usual method of preparing crude pollen extract. Therefore, if one uses the whole pollen the yield is six times as great and a broader antigenic preparation is obtained. The whole pollen granule can be used by converting it to the hydrochloride which can be sterilized by means other than filtration.

## PREPARATION

It is necessary to use a pollen collected within two years of the time of preparation of the pollen antigen. An older pollen will not form the hydrochloride as readily.

The ordinary method of defatting pollen (particularly ragweed) is not sufficiently complete. The pollen must be thoroughly and completely defatted. If this is not done, the residual fat will cause a local reaction.

The desired amount of completely defatted dried pollen is mixed with a sufficient amount of a solution of 10 per cent concentrated hydrochloric acid in 95 per cent ethyl alcohol. This treatment, which must be conducted in the cold, converts the pollen antigen to the hydrochloride within the pollen granule. Approximately forty-eight hours are required to complete the reaction. The pollen is then milled in a porcelain ball mill until the pollen granule is competey disrupted.

The pollen preparation is then separated by centrifugation, and the acid alcohol and soluble impurities completely removed by repeated washings. This is essential as any remaining acid alcohol or impurities will be irritating. The pollen is then suspended in physiologic saline solution, the pH adjusted to 6 to 6.5, and the preparation sterilized by one of the previously reported methods.[11,15,16] A preservative, such as 1:10,000 Merthiolate®, is added and the suspension diluted to the desired concentration.

The original pollen antigen hydrochloride (Delapan-Lilly) was standardized in Delapan units.[16] One Delapan unit is equivalent to three Noon units or two protein nitrogen units. It has been determined that a one and one-half per cent suspension of the whole pollen antigen hydrochloride is equivalent to 30,000 Delapan units per cc, 90,000 Noon units per cc, or 60,000 protein nitrogen units per cc.

## CLINICAL RESULTS

During the season of 1946, four cases were treated with the whole pollen antigen hydrochloride (Improved Delapan marketed by Hollister-Stier Laboratories). During the following seasons (1949-1950), an increasing number of cases were treated. The dosage schedule was the same as used for the original Delapan antigen.[11,12,16] The initial dose is usually 50 Delapan or 150 Noon units; and the dosage is rapidly increased to a maintenance level of 15,000 Delapan or 45,000 Noon units. In 1951 the preparation was supplied to a number of doctors. Our own results and those of the reporting clinicians have been gratifying. A series of 317 cases treated and followed by Dr. Charlotte Wiedemer, Chief of the Allergy Service, Cincinnati General Hospital, is reported in Table I.

Dr. Wiedemer reported an undue number of reactions which she did not observe with Lilly's original Delapan. These were mainly local reactions which often persisted a considerable time. Unfortunately all of the preparation used in this series was made in 1951 before it was realized that the fat had to be completely removed. At first it was felt that a little fat might be beneficial. These local reactions, however, were undoubtedly due to the fat content of the preparation.

## COMMENTS

Whole pollen antigen hydrochloride is the most complete pollen antigen preparation which has been reported. Due to this and the fact that the

TABLE I. CLINICAL CASES TREATED WITH IMPROVED DELAPAN*

| Type of Treatment | No. Cases | | | Age | | Results | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Old** | New | Maximum | Minimum | Excellent | Satisfactory | Poor |
| Ragweed 1951 Pre-seasonal | 42 | 32 | 10 | 73 | 5 | 12 | 28 | 2 |
| Ragweed 1952 Pre-seasonal | 48 | 36 | 12 | 73 | 4 | 22 | 25 | 1 |
| Ragweed Perennial | 64 | | | 77 | 3 | 44 | 18 | 2 |
| Ragweed 1951 Co-seasonal | 22 | 3 | 19 | 54 | 6 | 1 | 9 | 12 |
| Ragweed 1952 Co-seasonal | 18 | 5 | 13 | 42 | 6 | 2 | 6 | 10 |
| Grass 1951 Pre-seasonal | 30 | 18 | 12 | 73 | 3 | 20 | 9 | 1 |
| Grass 1952 Pre-seasonal | 36 | 22 | 14 | 73 | 4 | 30 | 6 | 0 |
| Grass Co-seasonal | 12 | 2 | 10 | 54 | 5 | 4 | 6 | 2 |
| Grass Perennial | 45 | | | | | 42 | 3 | 0 |

*Cases treated and followed by Dr. Charlotte Wiedemer, Cincinnati General Hospital, Cincinnati, Ohio.
**Those cases treated in previous years.

hydrochloride is relatively insoluble, this antigen has the following advantages:

1. It retains its potency much longer and is more uniform from lot to lot than other preparations.
2. Because this antigen includes the pollen granule and contains all the pollen antigens, desensitization should be more complete with consequently better clinical results.
3. This preparation is in the form of the hydrochloride which is mostly in suspension with only a very small amount of antigen in solution. This results in slow absorption.
4. Because it is slowly absorbed, it permits larger and more rapid increase in doses with less danger of generalized reactions.
5. This higher dosage may result in better protection.

## SUMMARY

1. The preparation of the broadest pollen antigen known is described.
2. Because this antigen as the hydrochloride is relatively insoluble, it has numerous advantages.
3. The clinical results of 317 cases treated with this antigen are given.

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## AUTOVACCINE IN TREATMENT OF ASTHMA

Two types of asthma have been distinguished: extrinsic and intrinsic. In extrinsic asthma the allergen comes from the outside. In intrinsic asthma bacterial products originating in a focus of infection within the body act as the allergen. In this group vaccine treatment has long been known to be effective. Bergquist reviews observations in the treatment of 341 patients with asthma, of whom 189 were classified as having intrinsic and 152 as having extrinsic asthma. Those with extrinsic asthma were treated by means of specific hyposensitization followed by nonspecific hyposensitization in the form of autogenous vaccination. When the patients with intrinsic asthma reacted positively to cutaneous tests, both specific and nonspecific hyposensitization was induced, while the negative reactors to cutaneous tests received only autovaccine. The therapeutic results were good in 80.4 per cent of the patients with the intrinsic and in 71.7 per cent of the patients with extrinsic asthma. There is no significant difference in therapeutic response between males and females, but age is important. Children show the best results, and the good results decrease with advancing age.—*Acta med. Scandinav., 144:81-164 (No. 2) 1952. Abstracted from J.A.M.A. (Apr. 11) 1953.*

# FOOD-INDUCED, ALLERGIC MUSCULOSKELETAL SYNDROMES

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INGESTION of allergenic foods can produce a variety of musculoskeletal syndromes in susceptible individuals. This paper describes the clinical features of such disorders as they were observed in a group of forty-seven patients, ages ranging from twelve to seventy-six, who consulted me during the past ten years.

Allergic musculoskeletal disorders occur when specific offending foods are eaten in threshold amounts and vanish when these foods are excluded from the diet. Although this operational definition is simple, the correct diagnosis and subsequent identification of offending foods is sometimes difficult. The signs and symptoms may be confined to muscles or joints, or may involve both muscles and joints. When musculotendinous structures are largely affected, the term allergic rheumatism has been used; and when articular tissues are largely affected, the term allergic arthritis has been used.

These allergic musculoskeletal syndromes may occur as isolated episodes, or as a steady state of discomfort, with or without periodic exacerbation and remission of symptoms.[5] These syndromes may occur alone or in association with any other form of allergic or non-allergic disease.

Allergic muscular disorders include two chief clinical conditions: the fatigue syndrome and the pain syndrome.[6,9,10]

Patients who have the allergic fatigue syndrome complain of overwhelming fatigue. Mentally they are alert. They have no pain. They may have an associated lymphadenopathy, lymphocytosis and eosinophilia. Hypothermia is common. But the outstanding clinical feature is hypotonia of somatic muscles and rapid exhaustion when any muscular work is undertaken. The muscles are not tender to palpation. Rest alone does not ameliorate the condition as long as the person continues to ingest the offending food.

Patients with the allergic pain syndrome[6] complain of regional or generalized muscle pain which is aggravated by somatic muscle contraction, work or pressure. Such patients move slowly to avoid an exacerbation of pain which may result from rapid muscular contraction. They often avoid unnecessary physical exertion. They try to keep their muscles as relaxed as possible, but palpation suggests that their somatic muscles are swollen. Hypertonia occurs promptly when the patient actively contracts his muscles, whereupon the muscle not only feels firmer than normal, but is often very

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Some medical writers have denied (1, 3, 4) and others have affirmed (1, 2, 6, 7, 8, 9, 10, 11) the existence of food-induced, allergic musculoskeletal syndromes. I believe that failure to understand the spontaneous clinical patterns of such allergic disorders has been responsible for these differences of opinion.

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tender to palpation. Although some patients also complain of fatigue, muscular pain is the outstanding feature of this allergic syndrome.

Sometimes, ingestion of an allergenic food may cause symptoms and signs limited to the periosteum, periarticular or articular structures. Arthropathy may be limited to a single joint or to several joints, or may be generalized.

Mechanical work tends to favor localization of the most severe allergic reactions in those joint structures subjected to the greatest amount of mechanical stress. But localization of signs and symptoms to a given joint may occur without apparent relationship to mechanical stress.[6]

Sometimes the patient will have only allergic arthralgia or a sense of stiffness on moving the affected joint, without objective evidence of joint involvement. This disappears when the offending food is eliminated from the diet, and reappears when threshold amounts of this material are ingested. Or the patient may have evidence of muscle spasm only in somatic muscles moving the joint elicited by rapid passive back-and-forth movement of the joint. There may also be swelling of the joint, which may be minimal, or may take the form of marked hydrarthrosis. Sometimes, the affected joint may be swollen, hot to the touch, and even red and very painful to move. Here, the causal agents seem to be the allergic reaction of joint structures, and mechanical trauma.

Rarely, only the periosteum or only the tendons are uncomfortable and tender to pressure, and this only after the patient has ingested a threshold amount of offending food.

It is important to realize that allergic articular reactions may occur in joints which are otherwise normal, in those afflicted by hypertrophic arthritis or rheumatoid arthritis, and in gouty joints.

*Case 1.*—Mrs. J., a forty-four-year-old woman had intermittent attacks of excruciating pain in her left hip, lasting four to eight hours at a time, then gradually subsiding. These episodes of pain bore no direct relation to any major life problems, although she seemed to have most episodes after attending parties. When I first saw her, she had had this condition for more than four years. She had been given injections, medications by mouth, diathermy treatment. A surgeon promised that treatment of varicose veins would cure her, but it failed to do so. Thereupon, he offered to do a hysterectomy "to see if this would cure" her, but the patient declined his offer.

When I examined her, her left hip moved freely. X-rays showed no evidence of bone and joint disease. Later I examined her during one of her attacks, and she had great pain. The large muscles of her thighs were in spasm, and when I opposed their contraction, I could move her left hip joint through the full ranges of movement, even though the pain was agonizing.

After analyzing her food-symptom diary, I suspected that she was sensitive to egg. I prescribed an egg-free diet and her symptoms disappeared for several years, save for those occasions when she accidentally or deliberately ate egg-containing foods.

After three years, she again started having attacks of left hip pain similar to her initial ones. Since she was not eating eggs, a search was made for other possibly

allergenic foods. She seemed to be allergic to grapefruit. This food was eliminated from her diet, and she was placed on a modified rotary diet, with no recurrence of symptoms.

*Case 2.*—Mr. M. was a fifty-five-year-old man with moderately severe hypertrophic arthritis of the spine and knees as revealed by x-rays. Clinically he had limitation of movement in nearly all of his movable joints. He complained of pain and stiffness in his shoulders, back and knees. Although it would have been easy to ascribe all his troubles to hypertrophic arthritis, clinical study revealed that he was allergic to milk. Elimination of this food from his diet resulted in relief of symptoms, slight improvement in mobility of his joints, but no change in his x-ray status.

This case illustrates how a concomitant food allergy may be the cause of troublesome symptoms in an individual with hypertrophic arthritis. By eliminating milk from the diet, his allergic musculoskeletal syndrome was subtracted, and the underlying hypertrophic arthritis was asymptomatic.

A similar situation may exist in patients with rheumatoid arthritis, rheumatic fever and gout. An allergic, food-induced musculoskeletal syndrome may be superimposed on these conditions. Elimination of the offending food gives some relief from some of the symptoms and signs even though the associated musculoskeletal diseases may be uninfluenced. This is different from the condition in which an attack of gout may be triggered off by a food allergy,[2] and different from the type of food-induced allergic musculoskeletal disorder which has the clinical form resembling rheumatoid arthritis.[12] In these instances elimination of the offending food may prevent, respectively, recurrence of the gouty attack or the allergic arthritis.

*Case 3.*—Mrs. L., a sixty-five-year-old woman, was employed as a pattern cutter. She used shears to cut stiff cardboard as part of her daily work, and her output varied little from day to day. She had mild hypertrophic arthritis of her hands. She rarely ate chocolate, but when she did after a latent period of twelve to eighteen hours she developed joint pain limited to her hands. Within twenty-four hours she developed red-hot, swollen, tender interphalangeal joints having a pattern resembling rheumatoid arthritis, and she felt generally tired and achy. Within four days, her condition would begin to improve, and within ten days she would again be well, i.e., as she was before ingestion of chocolate. When she ate chocolate during vacation periods, she had only joint pain in her fingers, achiness of muscles and joints, and fatigue.

It seems clear in this case that the combination of allergic joint reaction plus mechanical trauma gave a reaction localized to the finger joints resembling rheumatoid arthritis. But the allergic reaction alone produced only arthralgia.

## DISCUSSION

I have reviewed some common allergic musculoskeletal syndromes which can occur in susceptible individuals. Not every patient in this series had symptoms limited to joint structures or muscles. The same offending food which gives joint pain may also give gastrointestinal symptoms, hives, headaches or any other allergic reaction. In some other person, milk allergy

may produce the fatigue syndrome, beef may produce arthralgia, and lettuce may give gastrointestinal symptoms and he may have all three reactions when he eats a meal containing all three foods.

In the literature, there has been disagreement about the exact role which food allergy plays in the production of musculoskeletal syndrome. I believe this has resulted from a misunderstanding of the complexity of allergic reactions in the musculoskeletal system.

These disorders occur when one or more specific allergenic foods are ingested in threshold amounts, and vanish when these foods are excluded from the patient's diet. The noxious agent is not the amount of allergenic food eaten, but rather that unknown quantity, the threshold amount of food antigen penetrating the gastrointestinal mucosal vascular barrier.

The variable patterns of musculoskeletal syndromes can be explained in terms of characteristics common to all food-induced allergic reactions.[5] First, there is a latent period between ingestion of a threshold dose of the offending food and the first appearance of signs and symptoms. These increase in severity, reach a plateau and then subside. The total allergic reaction lasts a definite time and can be graded as mild, moderate or severe in intensity.

Some food-induced reactions occur rather promptly after ingestion of the offending food (ten to fifteen minutes); others occur after a considerable delay (twelve to twenty-four hours). Some reactions are short lived. Others may last for three or four days. As food is ordinarily eaten at regular meal times, it is only the long-lasting allergic reactions which are capable of being summated into a steady state reaction. Here, the offending food is eaten before the allergic reaction from the preceding ingestion has had time to subside. Exacerbations can be produced by more frequent feedings or larger amounts per feeding of the offending food than ordinarily taken. Likewise, remissions can be brought about by elimination of offending foods from the diet.

This means that allergic reactions in the musculoskeletal system may be short lived, may last for several days, or may be rather continuous, with or without exacerbations and remissions.

In the fixed type of food sensitization, one can regularly elicit a musculoskeletal syndrome upon ingestion of a constant threshold dose of offending food. In exquisitely sensitive patients, one can successfully use the blindfold test to prove that the clinical disorder is indeed caused by ingestion of the specific food.

In variable food allergy, the threshold for production of allergic symptoms changes from time to time. Here, when the patient is very sensitive, it becomes easy to precipitate a food-induced musculoskeletal syndrome. But his sensitivity can be decreased as a consequence of abstinence from the offending food, or a decreased intake. Such a patient may have muscle or joint symptoms, or both, when he drinks milk regularly, but not if he decreases either the amount or frequency of milk ingestion.

The clinician must also realize that these allergic musculoskeletal syndromes may occur in persons who have no other disease, or in those who have rheumatoid arthritis or hypertrophic arthritis and even in some patients who have gout,[2] rheumatic fever or lupus erythematosus. Elimination of the offending food does away with the allergic musculoskeletal syndrome, but does not cure disorders having other etiologies.

For all these reasons, the physician wishing to treat such patients successfully must learn to recognize the variability and the range of clinical pictures which can occur in these allergic disorders. ACTH or cortisone give relief in most instances for as long as they are used. But unless offending foods are eliminated, these allergic musculoskeletal disorders recur when the drug is discontinued. The most satisfactory treatment is to eliminate the offending food from the patient's diet and to use some form of a rotary diet. This may be a prolonged and difficult venture for both the patient and his doctor.

## SUMMARY

The ingestion of allergenic foods can produce in susceptible individuals a variety of musculoskeletal syndromes, which disappear when specific foods are excluded from the patient's diet.

The signs and symptoms may be confined to muscles or joints, or may involve both muscles and joints. These allergic musculoskeletal syndromes may occur as isolated episodes, or as a steady state of discomfort, with or without exacerbation and remission of symptoms. They may occur alone or in association with any other form of allergic or non-allergic disease. The variable patterns of these musculoskeletal syndromes can be explained in terms of characteristics of all food-induced allergic reactions.

Mechanical work tends to favor localization of the most severe allergic reactions in those structures subjected to the greatest mechanical stress. But localization of signs and symptoms to a given region may occur without a known cause.

ACTH or cortisone give relief in most instances for as long as these drugs are used but unless the offending foods are eliminated the allergic musculoskeletal disorder recurs when the drug is discontinued.

The most satisfactory treatment is to eliminate the offending food or foods from the patient's diet, and to use some form of the rotary diet to minimize the likelihood of recurrences.

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## EOSINOPENIA INDUCED BY EMOTIONAL STRESS

Eosinopenia similar to that produced by the injection of corticotropin or cortisone has been observed as a response to many types of stress. Dreyfuss and Feldman made eosinophil counts in the blood of thirty-one medical students immediately before they began their oral examination. Control counts were done exactly twenty-four hours later, thereby taking into account possible diurnal fluctuation in the individual. There was an average drop of 44 per cent in preexamination counts as compared with the postexamination counts. A low eosinophil count, apparently due to continued tension, persisted in a few students after the examinations. In a group of ten women admitted for diagnostic curettage, there was an average drop of forty-two per cent in their preoperation counts as compared with their counts taken on admission. The decrease in eosinophil counts in both groups is ascribed to the considerable emotional stress undergone in the two situations studied. The authors feel that emotionally induced eosinopenia can easily interfere with the evaluation of eosinophil counts taken in various conditions of stress or with study of the effect of the administration of drugs or hormones. This type of eosinopenic response might even partly account for the extreme variability of so-called normal eosinophil counts. On the other hand, emotional eosinopenia may well provide a means of following the emotional components in, for instance, the course of psychosomatic illness. This type of eosinopenia may illustrate the influence that the cerebral cortex exerts on the hypothalamic-pituitary-adrenal system, and is a model of a psychosomatic phenomenon.—*Acta med. Scandinav., 144:81-164 (No. 2) 1952. Abstracted from J.A.M.A. (Apr. 11) 1953.*

# POLLEN SURVEY OF WEST TEXAS

V. E. FRIEDEWALD, M.D.
Big Spring, Texas

DAILY POLLEN counts have been determined in this area for the past one and one-half years, including two consecutive weed seasons. The gravity method of sampling air was used. Thinly coated petrolatum glass slides were exposed to the air for twenty-four hour periods in a standard air sampling device[1] placed on the flat roof of a two-story clinic building

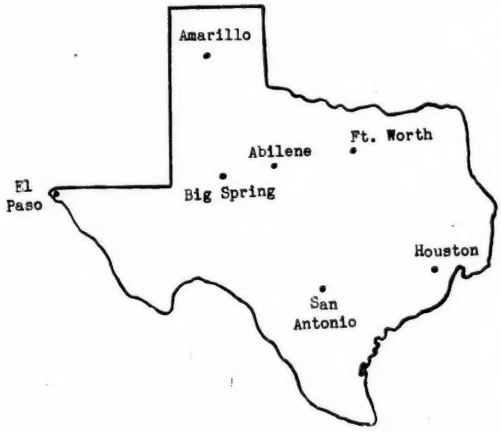


Fig. 1. Big Spring, Texas, Area.

located in the center of the city. The building is higher than any of the surrounding buildings and has an unobstructed roof except for one small penthouse. The slides were stained with Calberla's solution and the pollens found on 1 square cm area identified. Those of each species or allergically related group were counted separately. The number of pollen per square centimeter was then converted to approximate cubic yard equivalents as recommended by the Pollen Survey Committee of the Council on Aeroallergens of the American Academy of Allergy.[2]

This is the first pollen survey reported from this area. Pollen surveys have been reported from Fort Worth,[4] Abilene,[6] San Antonio,[5] and Amarillo.[7] Big Spring is 106 miles from Abilene, 263 miles from Fort Worth, 227 miles from Amarillo, and 306 miles from San Antonio (Fig. 1).

This part of the country had very little rainfall during 1952 (6.36 inches) and consequently vegetation was correspondingly less than other parts of the United States. Allergy patients, particularly those with asthma, often

migrate here to take advantage of the hot dry climate. Many are disappointed when little real benefit is noted. Often this is due to the presence of pollen to which they are sensitive in the air. Others quickly become sensitized to the local pollen, such as, mountain cedar or careless weed.

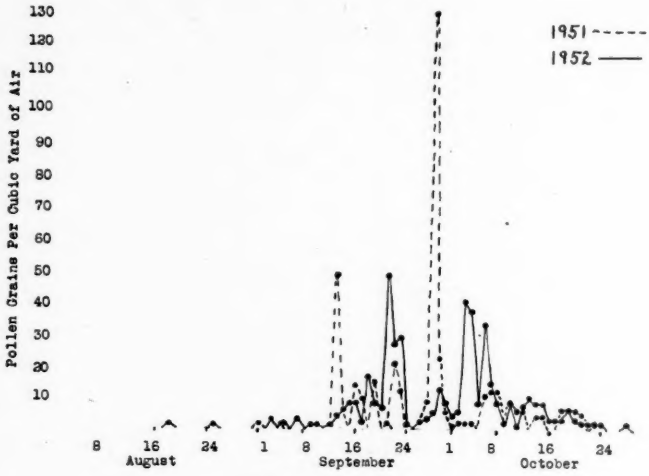


Fig. 2. Ragweed.

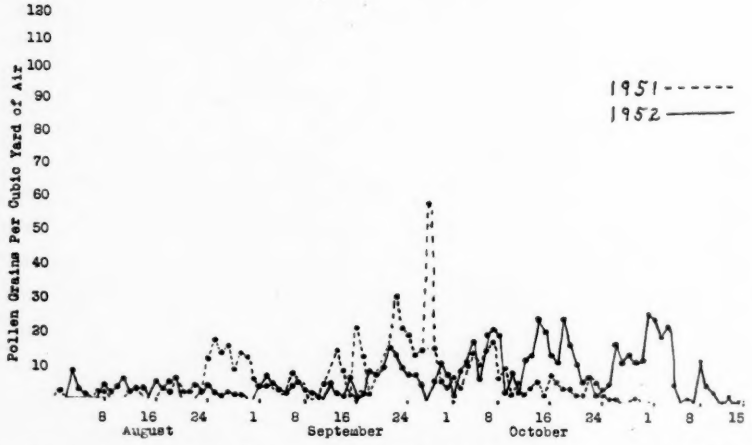


Fig. 3. Amaranth and Chenopod Weeds (Careless weed and Russian thistle).

The ragweed season is relatively mild as can be seen from Figure 2. The pollination period is mainly from the middle of September to the middle of October.

The amaranth weeds (Amaranthus Palmeri or careless weeds) and the

chenopod weeds (Russian thistle or tumbleweed) pollinate at the same time as the ragweed (Fig. 3) and far over-shadow the ragweeds in clinical importance. The amaranths and chenopods cannot be differentiated on the pollen slide, so they are grouped together. Both resemble dimpled golf

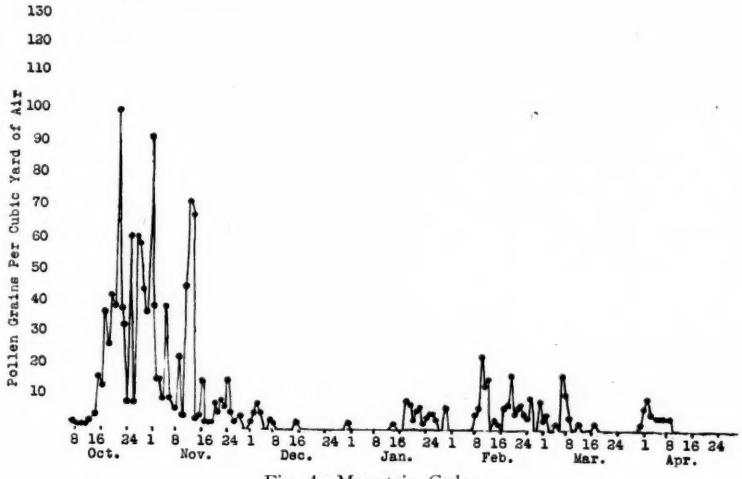


Fig. 4. Mountain Cedar.

balls microscopically. While the amaranths grow more abundantly around this area, the chenopods apparently have more toxic pollen, since Russian thistle (chenopod) leads the list of inhalant skin reactions in routine testing.[3]

Just as the ragweeds, tumbleweeds, and careless weeds are reaching the end of their season, mountain cedar (Juniperus sabinoides) pollinates and causes almost as much seasonal hay fever as the other three. From October to April, mountain cedar pollen is found on the slides (Fig. 4), but the highest counts are seen during October and November. This coincides with the time when mountain cedar hay fever patients are most affected.

Figure 5 indicates the mild winter and early arrival of spring last year in this area. Chinese elm pollen was seen on January 16, and pollination continued for several months. Chinese elm pollinated again in September.

Mesquite pollinates from the middle of April into June and accounts for some clinical allergy at that time (Fig. 6).

Grass pollen (Bermuda and Johnson) can be found on the slides from May until September, although in small amounts (Fig. 7). This, however, is misleading since Bermuda grass accounts for a large number of clinical allergies each summer. The discrepancy between pollen counts and number of clinical cases undoubtedly is due to the heavy exposure of patients to Bermuda grass lawns around their homes. The centrally located

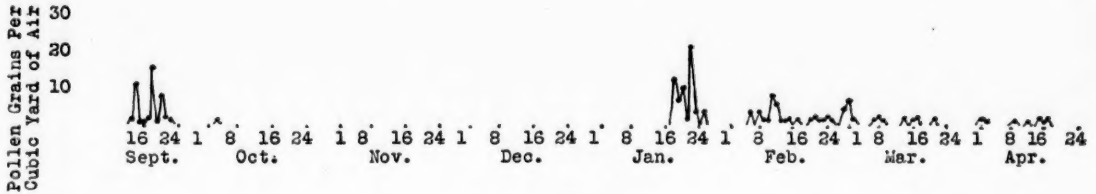
Pollen Grains Per Cubic Yard of Air
30
20
10
16 24 1 8 16 24 1 8 16 24 1 8 16 24 1 8 16 24 1 8 16 24 1 8 16 24 1 8 16 24
Sept. Oct. Nov. Dec. Jan. Feb. Mar. Apr.

Fig. 5. Elm.

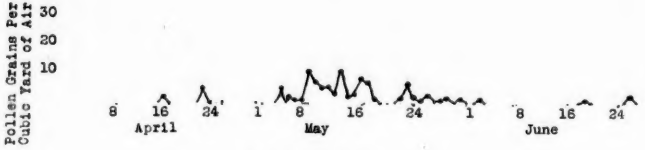


Fig. 6. Mesquite.

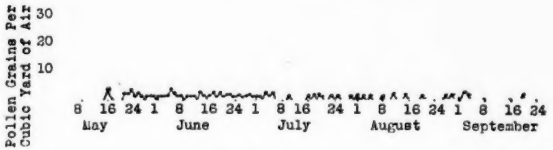


Fig. 7. Grass.

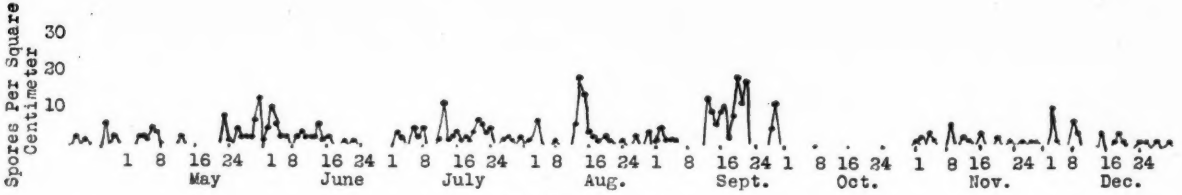


Fig. 8. Alternaria.

sampling device as used will not receive as much pollen as one placed on a lawn of Bermuda grass.

Figure 8 was included to indicate the Alternaria spores seen on routine air sampling. As will be noted, the spores are absent from January to April. While an occasional patient will be found clinically sensitive to Alternaria, it is certainly one of the rarer causes of inhalant allergy.

## SUMMARY

1. Three weeds pollinate in large quantities during September and October in this area—ragweed, careless weed, and tumbleweed.

2. Three trees are of importance—mountain cedar in October and November, Chinese elm in January and September, and mesquite in May.

3. Bermuda and Johnson grass pollinate from spring to fall.

4. Alternaria spores are found during all months except January to April.

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## ACA MEMBER ATTENDS EUROPEAN MEETINGS

Dr. F. W. Wittich, President of the International Association of Allergology, will attend the meeting of the Dutch Allergy Society, of which he is an honorary life Fellow, at Amsterdam and Groningen, May 14 to 16, 1953, prior to the meeting of the Second European Congress of Allergology, May 20 to 23, to be conducted under the auspices of the IAA at Copenhagen, Denmark. Speaking engagements have also been arranged in other countries.

# MÉNIÈRE'S DISEASE

## Case Report and Discussion

GEORGE R. LAUB, M.D., F.A.C.A.
Columbia, South Carolina

MÉNIÈRE'S disease is attributed to hemorrhages into the inner ear according to the original description by the author as related by most of the text books. However, Williams[18] in his excellent monograph on Ménières disease explains that "such a statement is contrary to the facts." According to him, Ménière wrote "that the physicians were lumping together all conditions which were characterized by vertigo, nausea and vomiting under the diagnosis of apoplectiform cerebral congestion, while he himself called attention to the inner ear as the site of the lesion in a number of cases." Ménière's original description has so completely covered the symptom-complex, that few new discoveries have been added. Lermoyez,[12] another Frenchman who did a great deal of work in the research of Ménière's condition, considers vasomotor ischemia of the labyrinth as the basis for this disorder which Eagle[5] considers a separate clinical entity. A number of other authors come to similar conclusions or put the syndrome on an angioneurotic basis. Runge[15] suggests the idea of "hydrops of the labyrinth." Halle,[8] and Grove Dohlman[4] classified Ménière's disease as an allergy; Eppinger and Hess[6] put forward the concept of vagotonia, a dysfunction of the autonomic nervous system.

Atkinson[1] made histamine tests and divided the cases into histamine sensitive and insensitive ones. In histamine sensitive cases headaches precede the attack and serve as an aura. In histamine insensitive cases or primary vasoconstrictor group, the headache is predominantly unilateral and on the deafer side, and follows instead of preceding the attack. Atkinson,[1] Vogel,[17] et cetera consider that there is a direct connection between Ménière's syndrome and migraine.

Bruehl[2] differentiates between "angioneurotic cochlearvestibular alteration and the real Ménières syndrome with hemorrhages into the labyrinth." According to Day,[3] an autonomic dysfunction or intrinsic allergy is the cause of the disease. Urbach[16] reports a case of extrinsic allergy. Hoogland[9] sums up the causes of the disorder due to disturbances chiefly in the vasomotor supply.

In reading the literature we are impressed by the different causes given, vasoconstriction, vasodilatation, allergy, histaminsensitivity, autonomic dystonia of the labyrinth, et cetera. Fowler[7] says "even these quoted causes are just sequelae of some other so far mostly still unknown causes." Kopetzky[10] even differentiates between Ménière's disease and Ménière's symptom complex or syndrome. In the latter there are no hemorrhages into the labyrinthine channels while in the former the actual lesion is such a hemorrhage. He classifies angioneurotic cases in a pseudo Ménière's symptom complex. This classification of Ménière's disease or syndrome does not agree with the general idea presented in the literature. According to this

author, vasomotor disturbances present a clinical picture of striking resemblance to Ménière's disease, but some of the main symptoms as tinnitus or deafness were absent; however, without deafness or some loss of hearing, the diagnosis of Ménière's disease should not be made. In this paper the discussion shall be restricted to allergy as the causative agent.

According to Von Pirquet,[14] an allergy is just an "altered reaction of the body to a foreign substance, the allergen." We know now that allergy may produce some local edemas, vasodilatation or vasoconstriction. Migraine which is recognized as allergic disease, can be treated successfully in some cases with desensitization measures. It can also be treated with histamine desensitization. However, it is interesting to note that some attacks can be stopped with Octin, which is a vasodilator substance." Were vasoconstriction the sole cause of Ménière's disease, a vasodilator should have the same effect as in migraine; however a number of experiments to that effect have been failures.[11] On the other hand we know that a number of allergic symptoms are caused by a dysfunction of one or more endocrine glands or by a disturbance in their correlation. This explains the favorable effect of Cortisone and ACTH in the treatment of allergic disorders. The same thoughts were already given in regard to Ménière's disease, but, so far as known to me, these hormones have not as yet been tested in its treatment.

Two cases with an allergic etiology are reported here in brief, omitting all the negative findings:

*Case 1.*—Mrs. M. B., No. 10828, was a forty-eight-year-old white woman, who had been in good health with the exception of some childhood diseases and frequent colds during the last few years. For the past two years she had noted a considerable loss of hearing in her right ear and complained that during that period she had had sudden attacks of vertigo, nausea and vomiting, which subsided after a short time. The attacks were so severe that she had to stay in bed until the dizziness disappeared. No medication was taken. Prior to her consultation the attacks had become more frequent, one or two a week, lasting an hour or more. The last one had lasted two days. Blood-pressure was 155/85 mm Hg. All the physical and laboratory findings were negative except for the following: 73 per cent hearing loss of right ear. 1 per cent hearing loss of the left ear, Weber, referred to the left.

The patient was given Nicotinamide and Anatola for ten days, when suddenly she had a severe attack of deafness, nausea, vomiting and vertigo. At this time she was hospitalized. Her deafness was of such a degree that it was impossible to communicate with her. She had severe nystagmus with the slow component to the right. Examination of the nose at that time showed bluish, edematous mucous membrane and turbinates, which made nasal breathing very difficult. Although there was no history of allergy, the patient was given Histadyl, intravenously and hypodermically. She improved very dramatically and within a little more than an hour her hearing returned to such a degree that it was once again possible to talk to her. At the same time her nausea, vomiting and vertigo ceased. After her discharge from the hospital she was given antihistaminic agents and stayed practically free of attacks. She had mild recurring episodes of the symptom-complex, but they have not been so severe. The patient was well enough to leave the city for a visit with relatives. She had been given an appointment to return for an allergy study. However, in the meantime she succumbed to an operation for an acute intercurrent disease. The postmortem showed no pathologic changes in the ears.

*Case 2.*—Mr. O. C., No. 9574, is a twenty-two-year-old white man who has suffered with hay fever for a number of years. His chief complaints were frontal headaches, watery discharge, postnasal drip, and occasional blockage of nose. He also complained of indigestion when eating certain foods. Otherwise he was in ex-

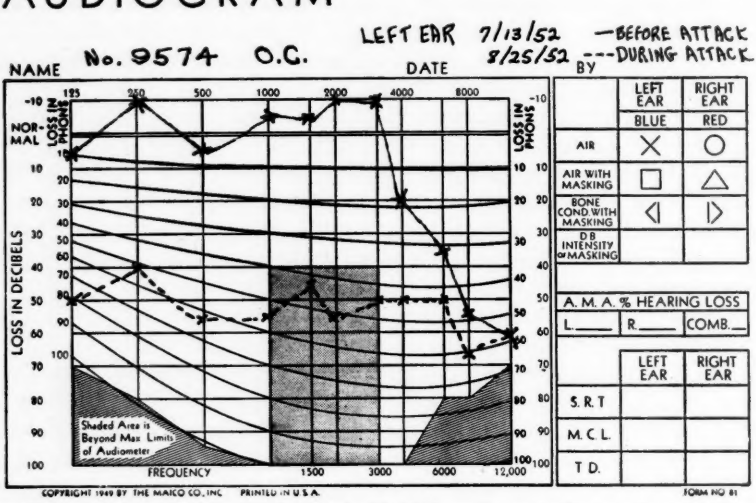


Fig. 1. Left ear before attack on July 13, 1952, same ear during attack on August 25, 1952. After attack the hearing returned to same as before.

cellent health. A few weeks before, for the first time he had an attack of vertigo, nausea, vomiting and deafness. At the time of his visit no pathologic change was found with the exception of those due to his hay fever. An audiometer test showed no loss of hearing in the left ear, and a 3 per cent loss in the right ear. Sometime later he returned at the time of an acute attack. It had just begun and the patient was dizzy and nauseated, with nystagmus and deafness. Now an audiogram revealed a hearing loss of 62 per cent in the right ear (Fig. 1). He was hospitalized, received Anatola, Histadyl and Nicotinamide and improved rather rapidly. Some weeks after the attack, and after discontinuing the medication, allergy tests were performed. He had a two to three plus reaction to some inhalants as grasses, weeds, feathers and some animal hair, and a four to five plus reaction to some foods as beef, and some spices. He was accordingly placed on a diet and received desensitization treatments for the inhalants. The patient has been free of any attacks for ten months. Some critics may consider that free interval as a natural remission. However, he had a number of such attacks in short intervals but since the treatment was started, not only has the ear condition returned to normal, but he has also had considerable improvement of his nasal allergy. During the last two months he has not adhered very strictly to his diet; nevertheless, he has had no recurrence.

These two cases are most likely caused by allergy. In the first case the negative autopsy report and the dramatic improvement with an antihistaminic agent are quite suggestive. It is also of interest that the hearing in an acute attack deteriorated to such an extent that it was impossible to

communicate with the patient by way of the spoken word. The second case improved nicely with treatment. Of course it is impossible to exclude a remission.

SUMMARY

Two cases of Ménière's disease are reported having an allergic etiology. The literature is reviewed briefly, and the different ideas of the causes of the Ménière's syndrome are discussed.

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# HAY FEVER IN IMMIGRANTS

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IT IS generally agreed that hereditary factors play an important role in allergic conditions. The incidence of a positive family history of allergy in allergic patients as given by most authors is about 50 per cent. Cooke and Vander Veer[1] reported a positive family history of allergy in 48.4 per cent of their allergic patients and only 7 per cent among their non-allergic controls. Spain and Cooke[5] found that 48.1 per cent of allergics gave a positive history of allergies, while Peshkin[3] reported that 42.57 per cent of allergics gave positive histories of allergies in their families. Feinberg[2] estimates the incidence of allergy in the families of allergic patients as 70 per cent.

Repeated observations confirm the fact that the incidence of a positive family history in hay fever patients is still higher. Kahn[6] states that 80 per cent of patients suffering from hay fever gave a positive history of respiratory allergies in members of their families, while Spain and Cooke[5] found that 58.4 per cent gave family histories of inhalant allergies.

Ratner[4] believes that heredity plays a minor role in the pathogenesis of allergy, and that the production of allergic syndromes is due to chance in that it depends on the amount of protein to which the individual is exposed, the state of permeability of the mucous membranes, the ability of the body to rid itself of invading protein substances and the intervals at which such exposures occur.

With these facts in mind, the authors felt that important information would be accumulated by comparing data obtained from individuals with late hay fever symptoms who come from countries known to be free of ragweed pollens, with data obtained from late hay fever sufferers born in the United States where ragweed pollens are known to exist.

The Allergy Clinic of the New York Hotel Trades Council and Hotel Association Health Center provides an excellent opportunity for the study of allergic conditions in immigrants, since a high percentage of its members are from abroad.

In order that the data accumulated would be most reliable, the immigrant patients, when necessary, were questioned in the language they could understand and in which they could converse the best. Since all of the members of the immigrant group under study had lived in this country for over ten years when this survey was made and are actively engaged in hotel work, which requires a good knowledge of our language, the authors

From The Allergy Clinic of The New York Hotel Trades Council and Hotel Association Health Center and City Hospital Allergy Clinic.

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had no difficulties in obtaining reliable histories, and feel that the information obtained from the immigrant group is as reliable as that obtained from those who were born in this country.

The following countries represent the birthplaces of the immigrants included in this study:

| Countries | Number of Patients |
|---|---|
| Italy | 26 |
| Poland | 26 |
| Russia | 21 |
| Germany | 18 |
| Ireland | 13 |
| Puerto Rico | 10 |
| Austria | 9 |
| Hungary | 7 |
| Spain | 6 |
| France | 4 |
| West Indies | 4 |
| Belgium | 3 |
| Greece | 2 |
| Rumania | 2 |
| Switzerland | 1 |
| Albania | 1 |
| Argentina | 1 |
| Holland | 1 |
| Lithuania | 1 |
| Turkey | 1 |
| Virgin Islands | 1 |
| Yugoslavia | 1 |
| British Guinea | 1 |
| England | 1 |
| India | 1 |

The largest number of immigrants under study suffering from hay fever came from countries which are known to be the richest sources of immigrants to the United States in the last four decades of this century; namely, Italy, Poland, Russia and Germany.

Statistical data pertaining to the following items were obtained from 162 immigrants with late hay fever and from 102 American-born hay fever sufferers:

1. Average age of the patients
2. Average onset of symptoms
3. Period of sensitization
4. Classification of each patient according to the skin reactions obtained on intradermal testings with various strengths of ragweed pollens
5. Incidence of allergic conditions in members of their respective families

Both groups in this survey approximate an average of over 80 per cent of all the cases of hay fever treated at the Health Center. The American-born patients in this study represent the "control group." The results of our findings are listed in Table I.

"Several significant facts are evident when we compare the statistical data obtained from the immigrant group of our late hay fever cases

TABLE I.

| | Immigrants | American-Born |
|---|---|---|
| Number of cases studied | 162 | 102 |
| Average age of patients | 47.1 yrs. | 39.0 yrs. |
| Average age of onset of symptoms | 35.3 yrs. | 24.6 yrs. |
| Period of sensitization | 15.8 yrs. | 24.6 yrs. |
| Per cent of class AA & A ragweed cases | 31.0% | 9.0% |
| Per cent of class B ragweed cases | 38.5% | 36.0% |
| Per cent of class C & D ragweed cases | 30.5% | 55.0% |
| Per cent of patients with positive histories of allergies in the family | 22.5% | 51.0% |

with those of the American-born group. The average age of the immigrant group at the time of our survey was 47.1 years, while that of the American-born patients was thirty-nine years. The average age of the immigrants at the time of their arrival to this country was 19.5 years. None had hay fever symptoms before they came to this country. The average age of onset of symptoms in this group was 35.3 years. Therefore, it took an average of 15.8 years (19.5 to 35.3 years) of exposure to the ragweed pollens in the United States before the late hay fever symptoms appeared in these individuals. This represents the time during which the immigrants were exposed to the ragweed pollens after which clinical symptoms of hay fever appeared, and can be designated as the period of sensitization. In the "control" or American-born group, the period of sensitization was longer—24.6 years.

Both groups were subjected to intradermal tests with various strengths of ragweed extracts and were classified accordingly. Those showing marked skin reactions to 1 and 10 protein nitrogen units of ragweed extracts (Noon units) were classified as AA and A ragweed cases, respectively; those showing marked skin reactions to 100 protein nitrogen units of ragweed extracts, as B cases, and those showing marked skin reactions to 500 and 1000 protein nitrogen units of ragweed extracts, as class C and D ragweed cases, respectively. In the immigrant group, 31.0 per cent were class AA and A ragweed cases as compared to only 9.0 per cent in the American-born group. Conversely, only 30.5 per cent of the immigrant group comprised the class C and D ragweed cases as compared with 51.0 per cent of the American-born group. These figures indicate that the immigrant group shows a higher degree of skin sensitivity to the ragweed pollens than the American-born group.

The percentage of immigrant patients with positive histories of allergies in their respective families is relatively low (22.5 per cent as compared with that of the American-born patients (51.0 per cent). This low incidence of inherited allergies in the immigrant group is contrary to the findings of the allergists of our country who made studies primarily on American-born individuals with hay fever. Our figure of 51.0 per cent showing positive histories in the families of our American-born patients with late hay fever is in agreement with the findings of most allergists.

## DISCUSSION

It is interesting to note that in the immigrant group with hay fever the onset of symptoms occurred later in life (35.5 years) as compared with the average age of onset of 24.6 years in the American-born patients. This is to be expected since the immigrants first came in contact with ragweed pollens when they arrived in the United States at the average age of 19.5 years, while the American-born individuals were exposed to these pollens from birth.

One can only speculate as to the reasons why the period of sensitization is shorter in the immigrant group of ragweed sufferers. This may be explained on the basis that the Americans born with allergic tendencies, who become sensitized to the ragweed pollens, develop more tolerance to the ragweed allergen. They have been exposed to it from birth and have developed their own specific antibodies to that allergen—nature's method of protecting them against noxious substances.

The lesser degree of intolerance to, or protection against, the ragweed pollen allergens in our immigrant group, makes itself more evident in comparing the reactions of the skins of both groups to the ragweed extracts. The immigrant group shows a greater degree of skin sensitivity to the ragweed extracts. This is indicated by a greater percentage of class AA and A ragweed cases in their group (31.0 per cent) as compared to 9.0 per cent in the American group; and, conversely, a lower percentage of the class C and D ragweed cases (30.5 per cent) as compared with the C and D ragweed cases (55.0 per cent) in the "control group."

The reason for the low incidence of positive histories of allergies in the antecedents of the immigrants with hay fever (22.5 per cent) as compared with those born in this country, may be explained on the basis that the antecedents of the immigrant group were not exposed to the ragweed pollens. In New York City a great majority of the patients with hay fever are cases due to sensitivity to the ragweed pollen. Generally, they consist of more than 75 per cent of all the hay fever patients seen in the Allergy Clinics in this country where ragweed pollens exist and the ragweed allergens are the major cause of seasonal respiratory allergies in these localities. One can with reasonable certainty state, therefore, that the lower incidence of inherited allergies in the antecedents of the immigrant group, as compared with those of the American-born group, is due to the fact that the parents of the immigrants were not subjected to the exposures of one of the most potent sensitizers of the respiratory system, the ragweed allergens, which cause such a high percentage of respiratory allergies in this country.

One must also be cognizant of the fact that the study of allergic conditions has advanced considerably more in this country in the last two or three decades than in the foreign countries, and that information concerning this subject has reached many more of the American physicians and

lay groups. Therefore, the diagnoses of allergic conditions are more frequently and earlier made in this country, and may also account for the lower statistical figures of initial histories of allergies in the antecedents of the immigrants.


## SUMMARY

A statistical survey was made on 162 immigrants with late hay fever symptoms, who came from countries known to be free of ragweed pollens, and 102 American-born individuals (control group) with the same condition.

1. In the immigrant group, the onset of symptoms occurs much later in life (average age 35.5 years) and is based on the fact that the immigrant group first came in contact with the ragweed pollens after they were adults.

2. The immigrant group shows a greater degree of skin sensitivity to the ragweed pollens, as indicated by (a) A greater percentage of class AA and A ragweed cases and a lower percentage of class C and D ragweed cases; (b) The period of sensitization is much shorter in the immigrant group. These facts indicate that the Americans born with allergic tendencies, who become sensitized to the ragweed pollens, develop more tolerance to the ragweed allergen since they have been exposed to it from birth and have developed their own specific antibodies to that allergen—nature's method of protecting them against noxious substances.

3. The immigrant group shows a lower incidence of positive histories in their respective families, which may be due to the fact that their antecedents were not exposed to the potent ragweed pollen allergens which are the cause of a majority of seasonal respiratory allergies in this country.


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# DRUG TOLERANCE IN ASTHMA

## Fatal Salicylate Poisoning from a Physiologic Dose

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SHOCK or death from physiologic doses of a drug is usually attributed to idiosyncrasy. Yet occasionally true poisoning occurs from relatively small doses, particularly of those drugs for which a wide variation of the minimal lethal dose is recorded. The minimal lethal dose of salicylates, for instance, when given orally ranges from 4 to 100 gm.

The following is the report of a fatal case from an intravenous injection of 2 gm of this drug. In order to explain the mechanism involved in the wide variation of the toxic threshold, experiments were carried out which will be related here.

*Case 1.*—A forty-eight-year-old woman had been under the care of a local allergist for two years because of bronchial asthma. This diagnosis was substantiated by repeated and strongly positive scratch and intradermal tests, by eosinophilia in the blood and in the respiratory secretions. A chronic sinus infection, verified by x-ray, had on several occasions complicated the clinical picture. The patient had been treated by eliminative procedures and injections of pollen extracts and respiratory vaccine. She was given an intravenous injection of 5 cc of a 20 per cent solution of sodium salicylate (1 gram). This drug had been recommended for the control of infectious sinus disease superimposed upon the allergic state. We ourselves had administered this medication approximately 100 times without any untoward effects other than the usual pain along the vein associated with the intravenous injections.* We had always taken the precaution of inquiring into sensitivity for acetyl-salicylic acid and coal tar derivatives and refrained from its use when such a history was elicited. This dose was repeated on July 11, when there was again evidence of an acute sinus infection. At this time she had her usual antigenic injection consisting of 12,000 units each of short and giant ragweed, 0.1 cc of respiratory vaccine, and 0.1 cc of rust extract to which she had previously given a three plus reaction.

On August 2, the patient was again seen with an acute sinus infection and thick yellow discharge from the nasal mucosa. There was no ill effect whatsoever from a repetition of the above injection, no blood at the site of injection and the local swelling from the injection was moderate. About thirty minutes later and just before leaving she asked for another injection of sodium salicylate since it had been so effective previously. Ten cc of the usual 20 per cent (2 grams) solution was then administered by the intravenous route during a period of about three minutes. Immediately upon withdrawal of the needle from the vein, she developed severe pain in the abdomen with marked respiratory embarrassment and cyanosis, tinnitus, general weakness, and a tendency to gasp for breath. She perspired profusely. The respiration rate was 42, the systolic blood pressure fell to 70 mm mercury, but the pulse rate remained at about 80. There was no urticaria, no increase of nasal discharge. She vomited repeatedly and passed small amounts

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Dr. Blair is deceased.

*This case was observed before antibiotics were known.

of urine frequently. The chest examination revealed a minimal number of moist râles but no asthmatic wheezes.

The patient was immediately given about 3 cc of epinephrine in fractional doses, the first one being 1 cc and on two occasions 0.1 cc intravenously. Not the slightest response was noted to this drug. Caffein sodium benzoate (15 gr) and 1 cc of coramine were given intramuscularly. Two grams of sodium bicarbonate was then injected intravenously in 150 cc of a 5 per cent dextrose solution. When no rallying tendency was evident after three hours, the patient was admitted to a local hospital where the following additional measures were employed. Epinephrine, external heat, intravenous glucose (500 cc of a 5 per cent solution), oxygen tent and caffein sodium benzoate. She also received a blood transfusion of 250 cc. Pain and tenderness in the region of the stomach associated with restlessness and dyspnea, frequent urination, occasional vomiting and gradual increase of pulse rate remained the outstanding symptoms. She expired seven hours after the injection of sodium salicylate.

Autopsy (exclusive of head) revealed the following positive findings: The lungs were slightly enlarged; the right weighing 800 grams and the left 645 grams. On cut section, fluid could be easily expressed and the whole of both lungs appeared watery. The bronchi contained large amounts of pink foamy liquid. The mucous membranes of the bronchi and trachea appeared slightly injected. A small amount of clear fluid was present in the pleural cavity. The aorta showed a minimal number of small atheromatous plaques. No thymic tissue was present. The mucous membrane of the fundic portion of the stomach had a sharply circumscribed area of intense hemorrhagic injection measuring about 10 cc in diameter. In the left ovary there was one small hemorrhage. The gall bladder contained a few small stones. All the other organs were grossly normal.

### SALICYLATE POISONING VS. ALLERGIC SHOCK

The distinction between anaphylactic shock and true intoxication from sodium salicylate is difficult, particularly when the course of the clinical picture is accelerated by the intravenous administration of the drug. That we are here dealing with true salicylate poisoning is indicated by the following facts:

1. The syndrome of allergic shock is dominated by dyspnea resulting from pulmonary edema or severe asthma which may or may not be associated with urticaria of skin and mucous membranes.[1] Instead of these manifestations, the outstanding signs here were abdominal pain, fast and deep respiration, and perspiration.

2. At autopsy, gastric and intestinal hemorrhages which were present are considered typical of sodium salicylate poisoning.[4,5] In allergic shock, evidence of capillary permeability in the lungs, extravasation of blood cells into the alveolar spaces and petechial hemorrhages in the lungs as well as in other viscera are characteristic.[1]

3. The effect of epinephrine is probably the chief distinguishing criterion: In allergic shock following an intravenous injection events occur so rapidly that complete collapse with cessation of respiration and heart action occur almost immediately. Yet, if the patient has been pulseless for several minutes, the administration of epinephrine, especially in small doses intravenously, induces a noticeable response. If these patients sur-

TABLE I. AVERAGE VALUES OF THE MINIMAL LETHAL DOSES FOR SODIUM SALICYLATE IN THE FOUR GROUPS OF TEN GUINEA PIGS

| | A | B | C | D |
|---|---|---|---|---|
| | Normal Guinea Pigs | Sensitized to Horse Serum | Sodium Salicylate Previously | Horse Serum and Sodium Salicylate Previously |
| Per Gram of Body Weight of Guinea Pig | 1.063 mg. or 100 per cent | .6116 mg. or 57.5 per cent | .8206 mg. or 77.1 per cent | .9200 mg. or 87.4 per cent |

vive as long as sixty to ninety minutes there is no more danger of death from allergic shock other than by a complicating pneumonitis.[2] For seven hours before death this patient did not show the slightest response to repeated injections of epinephrine, which is definite evidence that this is not allergic shock.

On two occasions, fifty-nine and twenty-one days previously, the patient had received one-half of the fatal dose without suffering the slightest ill effect. The intolerance to the drug therefore must have developed very recently; this could have been either the result of the previous administrations of the drug or of a depression of the patient's general resistance, associated perhaps with her particular state of sensitization. In order to investigate these two possibilities, the following experiments were carried out.

## EXPERIMENTAL EVIDENCE

The minimal lethal doses of sodium salicylate were determined in four groups of female guinea pigs, each consisting of ten animals, by injecting a solution of 13 per cent of this drug intravenously. The injections were made, without local or general anesthesia, from a calibrated burrette into the external jugular vein at a regulated rate never exceeding fifteen drops per minute. Group A consisted of normal animals. In group B an attempt was made to induce a state of sensitization by the intraperitoneal injection of 2/100 cc of normal horse serum twenty-one days previous to the injection of the drug. The ten animals of group C received ½ cc of 5 per cent sodium salicylate three weeks previously, in order to determine whether or not a previous administration of the drug would alter the lethal threshold. The animals of group D were given both the preliminary dose of sodium salicylate and the sensitizing dose of horse serum twenty-one days in advance. Here we attempted to simulate conditions in the patient who was both in a state of sensitization and had had previous injections of the drug. The average values for each group are charted in Table I.

The first sign of poisoning in the guinea pigs was a sudden decrease in rate and amplitude of respiration which lasted from ten to fifteen seconds. Occasionally complete cessation of breathing occurred for as long as ten to fifteen seconds. The respiration then gradually returned to a faster

rate but with shallow amplitude. Increased muscular irritability was noticeable by the appearance of tremors, and the twitching of all extremities when the animals were touched. Fecal and urinary incontinence occurred. Terminally the breathing became labored and thoracic in type. The injections were stopped when terminal symptoms were first evident. In all the four groups the mode of death was identical. The average time required for death was 53.3 minutes. At autopsy, hemorrhages in the gastrointestinal tract were present in four animals. No other organs were involved except for some passive congestion in the lungs.

In the normal animals (A), the average minimal lethal dose was 1.063 milligrams per gram of body weight. In the animals which had the previous injections of serum (B), only 57.5 per cent of this dose, namely .6116 milligrams per gram of body weight, was required to induce fatal intoxication. In group C, which had previously had sodium salicylate but in which no sensitization to foreign protein existed, the average minimal lethal dose was .8206 milligrams for each gram of body weight or 77.1 per cent of that required for the normal guinea pigs in group A. In the last series (D) in which both sodium salicylate intravenously and horse serum intraperitoneally had been given, the average minimal lethal dose was .9300 milligrams per gram of body weight or 87.4 per cent of that for the normal guinea pig in group A.

In adapting these experimental findings to a person of the weight of this patient (140 lbs.), the minimal lethal dose of sodium salicylate by the intravenous route would be 74.4 grams for a normal individual, 42.8 grams for a "sensitized" individual, 57.4 grams if a previous injection of sodium salicylate had been given, and 65.1 grams if the individual had been previously sensitized to horse serum and had previously had sodium salicylate.*

## DISCUSSION

Salicylates are well suited for this study because they are considered more dangerous in allergic patients than other drugs. These experiments, as well as the case recorded above, suggests that both a state of sensitization and a previous administration of sodium salicylate, lower the lethal threshold of this drug. In an allergic individual caution is therefore necessary not only because of danger of allergic shock but also because of the possibility of enhanced toxicity from the same dose. That this may also apply to other drugs was indicated to us by the observation of two asthmatics (L.S. and E.P.L.), in whom intoxication from "physiologic" doses of drugs appeared highly probable. Both patients died under identical circumstances following the ingestion of 1½ grain of sodium amytal and ⅓ grain of pantopon respectively. They

*These values are considerably higher than the minimal lethal dose in men.[3] This is probably accounted for by the variations in tolerance for different species of animals.

became semicomatose and gradually expired in deep coma with no apparent manifestations of dyspnea. Partial autopsy was obtained in case E.P.L. disclosing that death was not due to asthma.

It has been observed clinically that administration of a drug within a few weeks before has, under certain circumstances, induced sensitivity to the drug, manifesting itself in allergic shock. The above evidence derived from forty animals indicates that untoward effects from lowering of the toxic threshold may have to be reckoned with even in a normal individual if he had a previous administration of the drug several weeks before. Confirmation of our experimental data by others would therefore assist in the explanation of sudden death, not otherwise accounted for.

## SUMMARY

1. A case of fatal poisoning from an intravenous injection of 2 grams of sodium salicylate in an asthmatic person is reported.

2. Experiments carried out on forty guinea pigs indicate that the lethal threshold of this drug is lowered if the animals have been sensitized to horse serum, if a previous injection of this drug has been given, or if both sodium salicylate and horse serum have been given before.

3. Attention is drawn to possible fatal intoxication from a "physiologic" dose of a drug. This should be borne in mind in unexplained death in an allergic person or in a normal individual who has had a recent administration of the same drug.

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# USE OF CHLOR-TRIMETON MALEATE® INJECTABLE IN BLOOD TRANSFUSIONS

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THE DISCOVERY of the Rh factor, refinements in blood typing technique, and the widespread use of disposable transfusion sets, have all materially contributed to reducing the incidence of transfusion reactions. Fortunately, severe or fatal reactions of the hemolytic or anaphylactic type are uncommon. However, allergic or pyrogenic reactions consisting of chills, fever, hives, angioedema, pruritus, tightness of the chest, asthma, or other symptoms occur in 4 to 7 per cent of the cases recently reported.[1,2] Reactions of this type are distressing to both patient and physician.

It would be desirable to eliminate any type reactions in patients undergoing transfusion. The similarity of some transfusion reactions to clinical allergic states suggests that antihistaminic agents may be helpful in preventing such reactions. A report[2] in the literature confirms this view.

Chlor-Trimeton Maleate injectable* was the antihistaminic agent employed in this study. From July, 1952, to October, 1952, 20 mg. were added to each unit of blood prior to transfusion. During October, 1952, to February, 1953, we reduced the dosage of Chlor-Trimeton to 10 mg per unit of blood, this amount being considered adequate. The Chlor-Trimeton Maleate may be added directly to the blood without any deleterious effect.

This series includes a total of 592 transfusions given at the Fairfield Memorial Hospital, Fairfield, Illinois, from November 1, 1951, through January 31, 1953. Patients were utilized from all services including surgical, medical, obstetric, and pediatric. From November 1, 1951, to June 30, 1952, 222 pints of blood were administered, without Chlor-Trimeton. From July 1, 1952, through October 30, 1952, 200 pints of blood containing 20 mg Chlor-Trimeton were given. Beginning November 1, 1952, alternate pints of blood that left the laboratory had 10 mg Chlor-Trimeton added. From November 1, 1952, through January 31, 1953, there were eighty-four pints of blood given with Chlor-Trimeton 10 mg and eighty-six without. Thus, for fifteen months a total of 284 pints of blood were given with Chlor-Trimeton and 308 without.

Any reaction occurring was treated by immediate cessation of the transfusion and appropriate symptomatic therapy. Whenever a reaction occurred, the blood was retyped. Reactions such as neckache, mild sweats, and temperature of 100°F. were recorded as definite reaction. Several illustrative case histories follow.

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*Supplied by the Clinical Research Division of Schering Corporation through the courtesy of George Babcock, Jr., M.D.

*Case 1.*—G. J. had had a cesarean section. One pint of blood with 10 mg Chlor-Trimeton was given after being in refrigeration in the Obstetric Department three days. Reactions consisted of fever, headache, chills, all subsiding with aspirin, warm blankets, and 20 mg Chlor-Trimeton subcutaneously.

*Case 2.*—M. B. had had an incomplete abortion and received six transfusions in two days. With the five pints of blood containing Chlor-Trimeton, no reactions occurred. However, with the one transfusion not containing Chlor-Trimeton, the patient developed fever, chills, neckache, sweats, and mild shock. Blood was retyped and had been correctly matched. The patient recovered after six hours of symptomatic treatment.

*Case 3.*—J. S. was a patient with a hemorrhaging peptic ulcer. He received seven transfusions; then had a gastrectomy two weeks later. Postoperatively he vomited large quantities of blood, and after continuous transfusing was reopened and his stomach re-explored. Bleeding was stopped and he recovered. Altogether this patient received a total of thirty-two pints of blood. He suffered two reactions—one mild and one severe, the latter resulting in a mild state of shock. Neither of the two pints of blood causing reactions had Chlor-Trimeton added, these two, plus three other pints, were the only ones he received without Chlor-Trimeton. The other twenty-seven pints of blood each contained 20 mg of Chlor-Trimeton Maleate Injectable.

## RESULTS

From November 1, 1952, through June 30, 1952, we administered 222 pints of blood without Chlor-Trimeton Maleate. There were seven reactions. From July 1, 1952, through October 30, 1952, we administered 200 pints of blood to which 20 mg Chlor-Trimeton had been added. There was one reaction. From November 1, 1952, through January 30, 1953, eighty-four pints of blood containing 10 mg Chlor-Trimeton were given. There was one reaction, which was due to mismatched blood. Among the eighty-six pints administered without Chlor-Trimeton there were five reactions, also including one due to the wrong type blood.

## CONCLUSIONS

Chlor-Trimeton Maleate injectable when added to blood decreased the frequency and severity of allergic and pyrogenic transfusion reactions. In this series the incidence of such reactions was 3.5 per cent in the control group compared to 0.3 per cent in the treated group. No reactions attributable to Chlor-Trimeton Maleate were noted. The results of this study suggest that the routine prophylactic use of Chlor-Trimeton Maleate injectable in blood transfusion is a worthwhile procedure.

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# RESPIRATORY ACIDOSIS—PATHOGENESIS AND TREATMENT

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THE SYNDROME of "carbon dioxide intoxication" has been greatly discussed in the literature of recent years. It is felt by many, however, that "carbon dioxide intoxication" is a misnomer since the basic disturbing factor is "respiratory acidosis."

## MANIFESTATIONS OF RESPIRATORY ACIDOSIS

During the past decade man's longevity has increased and with this the incidence of chronic diseases has been more apparent. Patients with various degrees of chronic pulmonary emphysema are commonly encountered in all hospitals and are usually admitted because of acute respiratory distress with marked breathlessness and cyanosis. There may be evidence of superimposed pulmonary infection. Generally, the first medicament to be administered to such a patient will be oxygen in high concentrations or sedative drugs alone or in combination. The patient's color usually improves promptly and his dyspnea lessens, but central nervous system symptoms develop as the oxygen administration is continued—a real example of "paradoxical therapeutics."

These symptoms may be mild—weakness, headache, lassitude, irritability, personality and mood changes, or they may be severe—confusion, stupor, coma, and eventually death. Effective ventilation is markedly diminished during the later phases of respiratory acidosis characterized by these severe symptoms.

In order to understand the pathogenesis of respiratory acidosis, it is necessary to discuss the normal control of respiration and the homeostatic mechanisms involved in acid-base balance.

## CONTROL OF RESPIRATION

Under normal circumstances, the stimulus for respiration is the so-called *"centrogenic drive,"*[6] that is, the influence of partial pressure of carbon dioxide and the pH of the blood on the medullary respiratory centers. Changes in the partial pressure of oxygen appear much less important in normal individuals. When for any reason there is defective gas exchange in the lungs, with hypoxia and increased arterial $pCO_2$ (hypercapnia) persisting for some time, the medullary centers lose their sensitivity to carbon

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dioxide. The centrogenic drive then appears to play a minor role in sustaining respiration. Instead, the *"chemoreflex drive"* takes over, i.e., the effect of hypoxia on the carotid and aortic chemoreceptors is predominant in stimulating the medullary respiratory centers via the ninth and tenth cranial nerves respectively.

## NORMAL ACID-BASE BALANCE

The blood plasma is normally slightly alkaline in reaction, the hydrogen ion concentration ranging from pH 7.38 to pH 7.42. Remarkably efficient mechanisms maintain the hydrogen ion concentrations within extremely narrow limits in spite of constant fluctuation in the amount of acid and base substances, both endogenous and exogenous, which occur in normal and pathologic states.

These mechanisms consist of (1) *Buffer systems* in the blood and tissues which act immediately in any sudden alteration of the proportions of acid and base, and (2) *Excretory processes* which eliminate the excess acid or base as the next step, restoring the equilibrium to its previous state. The buffer systems are (a) bicarbonate, (b) phosphate, and (c) plasma proteins, hemoglobin, and chloride. The excretory systems are (a) the lungs, (b) the kidneys, and (c) in a minor role, the gastrointestinal tract.

The bicarbonate system consists of a mixture of carbonic acid ($H_2CO_3$) and bicarbonate salts ($BHCO_3$), mainly, those of sodium and potassium. The hydrogen ion concentration depends on the ratio of the acid to the salt, $\frac{H_2CO_3}{BHCO_3}$, and varies directly according to the formula $H = K \times \frac{HA}{BA}$, H being the hydrogen ion concentration, K a constant for each acid, HA the acid and BA its salt. This is usually expressed as the Henderson-Hasselbach equation, $pH = pK + \log\frac{salt}{acid}$. The efficiency of the system lies in the fact that carbonic acid is a weak acid, dissociating into few hydrogen ions, and that it is volatile, being quickly eliminated as carbon dioxide through the lungs. The addition of a strong acid, either endogenous or exogenous, to the body fluids brings about first its immediate neutralization as it reacts with the bicarbonate base to form its salt and then its replacement by carbonic acid which is a weak acid and can be excreted as $CO_2$ and $H_2O$. This loss of bicarbonate salt is normally equaled by the loss of carbonic acid, as carbon dioxide is expelled from the lungs, and the ratio of acid to salt remains unaltered, i.e., the pH remains the same. In a similar manner an excess of base will bring about an increase in bicarbonate and is matched by homeostatic mechanisms which increase carbonic acid through the retention of carbon dioxide; thus the acid to salt ratio remains the same, as does the pH. Conversely, any primary alteration in the amount of carbonic acid brought about by increased or decreased carbon dioxide excretion will cause an alteration in

the quantity of bicarbonate in order to maintain the normal ratio of acid to salt and the pH.

Since the blood bicarbonate represents a readily available supply of base for the neutralization of acids it has frequently been referred to as "alkali reserve." It must be pointed out, however, that this takes into account only one of its functions and does not warrant the assumption that a low alkali reserve must represent the presence of increased acids and a high reserve, an increase in body base. The assumption is true only when the first effect of any change in the quantity of acids in the body is on the bicarbonate portion of the buffer system, e.g., the ingestion of a strong acid; the changes in carbonic acid follow as a compensatory mechanism. Here the determination of the alkali reserve may be of value. However, when the first effect is on the acid portion of the buffer system, i.e., a change in carbonic acid brought about by a change in ventilation, and a parallel increase or decrease in the bicarbonate occurs secondarily, the measurement of blood bicarbonate is then a determination of a compensatory mechanism and the values move in opposite directions. The values obtained in such a case will be misleading, since they are reversed.

The phosphate system consists of a mixture of monosodium phosphate (a weak acid) and disodium phosphate (a salt) in a ratio of about one to four forming a buffer system which acts the same as the bicarbonate. This system operates primarily in the tissues, while the bicarbonate system operates primarily in the blood and to a lesser extent in the tissues.

Plasma proteins, which are amphoteric substances, act as weak acids in the alkaline medium of the plasma, holding base which is available for the neutralization of stronger acids. Hemoglobin, both reduced and oxygenated, similarly is a weak acid; a portion of it forms a potassium salt inside the red cell and it has a buffering action like bicarbonate and the others. Chloride must be included in the list because it extends the buffering action of hemoglobin in the "chloride shift."

These three groups are the important buffer systems of the body, holding the pH within a narrow range as ingestion, metabolism, and excretion —normal most of the time but occasionally pathological—constantly alter the quantities of acid and alkali. They work in unison so that if the values for one are known, the state of all of them is known. The base contained in all of them grouped together is called "buffer base" (abbreviated, especially for use on charts, as $B_B+$) and is a part of the "total base" (B+) which is the sum of all the cations (Potassium, Magnesium, Calcium and others). The difference between the two is the base tied up in neutralizing the fixed acids like sulfate, lactate, et cetera.

Of the excretory mechanisms the lungs are extremely important because they respond immediately to any changes in the acid-base balance of the body and either retain or excrete an acid as required. The level of the *volatile* carbonic acid in the blood is determined by the partial

pressure of $CO_2$ in the lungs. The respiratory center, controlling the rate and depth of breathing, can alter the $CO_2$ content of the lungs and therefore the blood carbonic acid level from breath to breath. Though the response to an increased level of carbonic acid in the blood is prompt, the lung is limited to one acid only in its function. The kidneys, on the other hand, though responding more slowly, are able to excrete *fixed* acids, bases, electrolytes, and metabolites which in any way might disturb the equilibrium of the body. The kidneys excrete selectively, retaining what is needed as far as possible.

## TYPES OF DISTURBANCES IN ACID-BASE BALANCE

The possible disturbances of the acid-base balance can be divided into two main groups: (a) metabolic and (b) respiratory. (a) Metabolic disturbances are best defined by the determination of whole blood buffer base ($B_B+$), the sum of the buffer cation concentrations, expressed as milli-equivalents per liter of plasma (mEq/L). Normal values range from 45 to 55 mEq/L.[21] Buffer base changes originate mainly from such metabolic processes as intestinal absorption and secretion, renal function, tissue metabolism, et cetera. Buffer base is not determined directly, but can be obtained from the nomograph of Singer and Hastings.[20]

(b) Respiratory disturbances are essentially reflected by the arterial partial pressure of carbon dioxide ($pCO_2$) expressed in mm Hg. The normal value is 40 mm Hg. This can be obtained directly by the Riley technique,[15] or indirectly from the Henderson-Hasselbach equation, knowing the pH and the carbon dioxide content of the arterial blood plasma. This determination is greatly facilitated by the use of the nomograph of Singer and Hastings.[20]

When the ratio of $\frac{H_2CO_3}{BHCO_3}$ is disturbed so that the hydrogen-ion concentration of the blood is maintained below the lower limit of normal, the organism is in a state of *uncompensated acidosis* (pH 7.30 or less). The most common clinical condition and the one of concern in this presentation, leading to a state of acidosis, is a primary excess of carbonic acid (carbon dioxide tension) of the blood: *respiratory acidosis.* Acid-base changes due to respiratory disturbances can be followed accurately only by the arterial $pCO_2$; changes in carbon dioxide content are a poor guide. The carbon dioxide-combining power is useless for the evaluation of the *degree* of respiratory involvement. The $pCO_2$ is rapidly altered by lung ventilation and represents the primary factor in assessing these respiratory changes.

Having determined the $pCO_2$ and buffer base ($B_B+$), the two so-called independent variables, one can follow the various types of disturbances of acid-base balance. At the outset, the disturbance is usually purely respiratory or metabolic. However, when present long enough to call

for compensatory mechanisms the disturbances become mixed. Figure 1,* based largely on Davenport's[8] concepts, helps to visualize these changes graphically. A, B, C, and D represent four *pure* types of acid-base disturbances before any compensation takes place.[18] The areas below

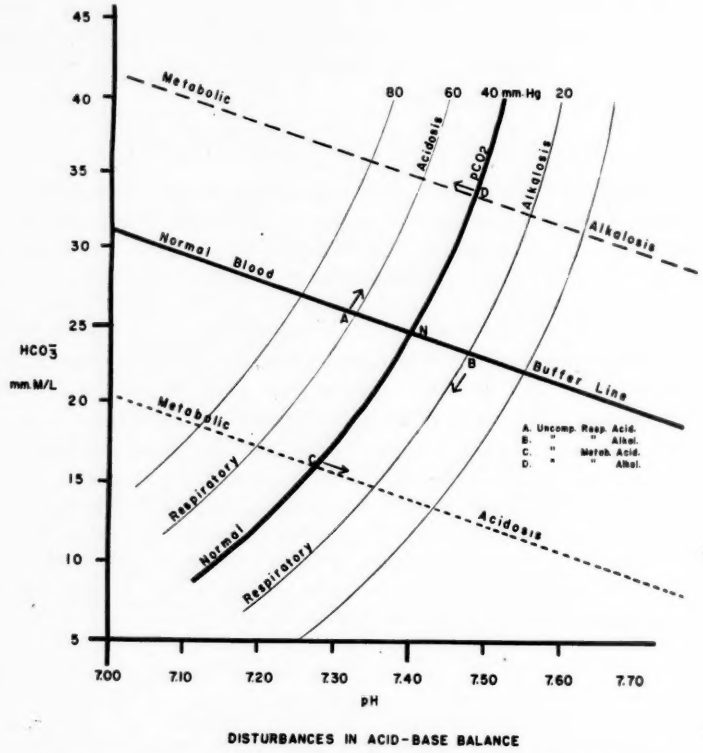


Fig. 1. Graphic presentation of acid-base disturbances. Point A shows a high $pCO_2$, a high bicarbonate content and a low pH, i.e., respiratory acidosis. The arrow at point A indicates the direction of the compensatory changes in order to restore a normal pH when the patient is unable to lower the $pCO_2$ to normal.

and above the normal blood buffer line indicate metabolic acidosis and alkalosis, respectively, while the $pCO_2$ isobar of 40 mm Hg separates respiratory acidosis to the left from respiratory alkalosis to the right. The direction of the arrows indicates the way which the compensatory mechanisms follow in order to restore the basic homeostasis. A patient in respiratory acidosis (A) is fixed on a high $pCO_2$ level, has a low pH

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TABLE I. PATHOGENESIS OF RESPIRATORY ACIDOSIS

| |
|---|
| 1. Chemoreflex and Centrogenic Drives |
| 2. Acute Relief of Hypoxia |
| 3. Decrease in Effective Alveolar Ventilation |
| 4. Increase in Arterial $pCO_2$ ($CO_2$ Narcosis?) |
| 5. Progressive Drop in Arterial pH (7.38 - 7.42) |
| 6. Drop in Cerebral $O_2$ Consumption |
| *Compensatory Mechanisms* |
| Progressive Metabolic Alkalosis: |
| Lowered Serum Chlorides |
| Increased Urine Chlorides |
| Increased Serum Bicarbonate |

and a high bicarbonate content. In the process of compensation, *secondary metabolic alkalosis* develops, tending to counteract displacement of pH. Serum bicarbonates are further increased along with excretion of chloride anions through the kidneys.

## PATHOGENESIS OF RESPIRATORY ACIDOSIS

The purpose of ventilation is effective gas exchange between the pulmonary alveoli and the pulmonary circulation. When the gas exchange is no longer effective, from whatever cause, there follows first arterial blood hypoxia. The carbon dioxide, having twenty times greater diffusability than oxygen, remains normal at first; but eventually hypercapnia (increased arterial blood carbon dioxide level) follows. At this stage there is *compensated* respiratory acidosis, the homeostatic balance is effectively maintained and the pH ranges at normal levels. However, when the body is no longer able to maintain homeostasis, *uncompensated* respiratory acidosis develops with a drop in the blood pH. The clinical manifestations of respiratory acidosis are now observed.

One of the most common conditions in which respiratory acidosis tends to develop is chronic pulmonary emphysema. As this disease progresses, there develops persistent hypoxia and hypercapnia. As explained above, respiration is maintained in these patients mainly by the hypoxic stimulus. When high concentrations of oxygen are administered in order to relieve hypoxia and cyanosis, the main stimulus to respiration is thereby removed. Respiration and ventilation decrease markedly, the carbon dioxide level rises, followed by compensatory mechanisms maintaining the pH within normal range; namely, a decrease in serum chlorides, with an increased urinary chloride excretion, sodium retention, and an increase in serum bicarbonate, i.e, *compensatory metabolic alkalosis.* However, if ventilation and effective gas exchange remain impaired much longer, the body can no longer maintain adequate compensation and the pH decreases below normal levels. The development of respiratory acidosis is facilitated if, in addition, respiratory depressing drugs are administered. Table I illustrates the factors involved in the pathogenesis of respiratory acidosis.

The mental symptoms that develop are believed by some to be due to actual carbon dioxide narcosis,[7,23] while Barach and others feel that they are caused by the decreased pH.[3,5] Hypoxia by itself will cause mental

TABLE II. ETIOLOGY OF RESPIRATORY ACIDOSIS

1. *Chronic (Organic) Lung Disease*
   (a) In the course of chronic pulmonary emphysema
   (b) Oxygen induced
   (c) Drug induced
2. *Chronic (Functional) Lung Disease*
   (a) Kyphoscoliosis
   (b) Progressive restrictive pachypleuritis
3. *Acute Respiratory Insufficiency*
   (a) Involvement of the respiratory center
   (b) Neuromuscular involvement
   (c) Drug intoxication
   Opiates
   Barbiturates
   Nitrous Oxide

symptoms. It has also been demonstrated that a drop in pH decreases the cerebral oxygen consumption.[12,13] At the critical level of 2.1 cc of oxygen consumption per 100 gm of brain tissue per minute (normal value 3.3 cc) unconsciousness will develop. In addition, the administration of high concentrations of oxygen, i.e., an increase in the partial pressure of oxygen, gives rise to cerebral vasospasm. This, too, perhaps, contributes to the central nervous system symptoms. Many patients can be found who have an increased carbon dioxide level but do not demonstrate abnormal mental symptoms as long as the pH is within normal range.

## ETIOLOGY OF RESPIRATORY ACIDOSIS

In Table II we have listed many of the common causes leading to respiratory acidosis. This may occur in the absence of lung disease, but poor ventilation and ineffective gas exchange are the basic causative disturbances. When respiration and ventilation are depressed either by drugs, such as opiates, barbiturates, or anesthetic gases, or by involvement of the respiratory center through infection or injury, respiratory acidosis may develop. Neuromuscular involvement, e.g., myasthenia gravis, or asphyxia will cause the same disturbances.

Chronic functional lung disease, for instance, kyphoscoliosis or restrictive pachypleuritis when severe enough to interfere with adequate gas exchange may lead to respiratory acidosis. Usually it is the addition of respiratory depressing drugs or a superimposed severe infection that disrupts the precariously maintained homeostasis.

Most commonly, respiratory acidosis develops in chronic organic lung disease, especially when associated with chronic hypoxia, as in chronic progressive pulmonary emphysema. Here again the development of acidosis may be precipitated by the administration of respiratory depressing drugs,[16,17] also by the administration of high concentrations of oxygen[2] and by superimposed acute pulmonary infection.[22]

## DIAGNOSIS OF RESPIRATORY ACIDOSIS

Although a tentative diagnosis of respiratory acidosis may be made on the basis of the clinical manifestations, the diagnosis can be made with certainty only by laboratory determinations. The carbon dioxide content and pH are determined on arterial blood or on venous blood which is

TABLE III. TREATMENT OF RESPIRATORY ACIDOSIS

1. *Preventive*
   (a) Early Recognition of Signs and Symptoms.
   (b) Avoid High Concentrations of Oxygen.
   (c) Avoid Respiratory Depressing Drugs.
   (d) Avoid Combination of B and C.
2. *Etiologic*
   (a) Drug Intoxication
      Opiates—N-Allylnormorphine.
      Barbiturates—Picrotoxin.
   (b) Acute Obstruction of Airways.
      Bronchoscopy.
      Tracheotomy.
3. *Symptomatic*
   (a) Mechanical Respirator.
   (b) Electrophrenic.
   (c) Artificial Pneumoperitoneum.
   (d) Graded Program of Oxygen Therapy.
   (e) Etiologic Treatments When Indicated.

drawn anaerobically. With these two determinations, the $pCO_2$ can be obtained indirectly from the nomograph of Singer and Hastings. The normal value for $pCO_2$ is 40 mm Hg, and for the blood pH it is 7.38 to 7.42. In respiratory acidosis, the $pCO_2$ may rise to 80 mm Hg or higher and the pH decrease to 7.30 or lower.

## TREATMENT OF RESPIRATORY ACIDOSIS

Table III lists the various forms of therapy employed in the management of respiratory acidosis. These may be divided into three general groups.

1. *Preventive.*—Realizing the conditions in which this syndrome is apt to occur, the physician should avoid high concentrations of oxygen and avoid respiratory depressing drugs. When oxygen must be given to a chronically hypoxic patient, it should be administered in a graded program, as suggested by Barach,[1,3] starting with low concentrations and increasing gradually every one or two days. It is best to employ a nasal catheter with humidified oxygen, starting with one liter per minute flows for the first day or two, and adding one liter flow each day. After a flow of six liters per minute has been reached, it is convenient to change from nasal catheter to the plastic open face tent (ABC Type).[19]

Sedatives and narcotics should be given with caution. Morphine should be avoided; Demerol can be used cautiously with slightly greater safety.

2. *Etiologic.*—The immediate cause of the respiratory acidosis should be determined and eliminated or counteracted. If the syndrome is caused by acute airway obstruction, immediate bronchoscopy or tracheotomy may be necessary. If due to hypoventilation secondary to oxygen therapy, the administration of oxygen should temporarily be discontinued. The effects of barbiturates are best combatted with Picrotoxin. When the syndrome is caused by opiates, N-Allylnormorphine (Nalline®) should be administered.[9,18]

Nalline® has been employed successfully to counteract the respiratory depression caused by morphine, Pantopon, Dilaudid, Demerol, Methadon, Metapon, Dromoran, and Codeine.[10,11] While others did not find Nalline

effective against the effects of ether, cyclopropane, and barbiturates, we have reported gratifying results against respiratory depression caused by barbiturates in two patients.[9] We have observed strikingly good effects in two patients treated with Nalline against the effects of morphine.

*Case 1.*—A seventy-eight-year-old woman was given 30 mg of morphine sulfate for the relief of pain due to an incarcerated femoral hernia. Severe respiratory acidosis and coma followed shortly. Her respiratory rate was three per minute, the $pCO_2$ was 95 mm Hg, and the pH was 7.10. Nalline was administered in a total dose of 25 mg over a period of 157 minutes. The patient's minute ventilation increased immediately upon the intravenous administration of Nalline and was followed promptly by a decrease of the $pCO_2$ and a rise of the pH. The acid-base balance was completely restored after seventy-seven minutes.[9]

Each dose of Nalline was followed by an immediate increase in the rate and sometimes the depth of respiration. By changing the rate of the Nalline intravenous drip, an immediate parallel response on respiratory rate was noted. This may be interpreted as a direct stimulating effect upon the respiratory center rather than destruction of morphine by Nalline. Investigations by others postulated that Nalline acts as an antidote for morphine through an enzymatic destruction of the drug.[14]

Administration of Nalline by continuous infusion, after an effective single intravenous dose has been given, appears to be the treatment of choice. The infusion should be continued until a sustained response is obtained. This would also counteract any delayed release of morphine into the circulation from tissue depots.

3. *Symptomatic.*—Whatever the etiologic cause, respiratory acidosis follows depressed or ineffective ventilation. While the body reacts with compensatory metabolic alkalosis, the physician must react by attempting to establish more effective ventilation. The use of a body respiratory chamber, or preferably intermittent positive pressure breathing—inspiratory, should be considered, if available. In the patient with severe pulmonary emphysema the institution of a pneumoperitoneum may prove a real emergency life-saving procedure. The elevation of the diaphragm and establishment of a more effective respiratory mid-position improves the ventilatory efficiency of the lungs. Cyanosis will clear as the minute ventilation improves; however, it may be treated simultaneously with oxygen, employing a graded program of increased concentrations as previously described.

The value of intermittent positive pressure breathing—inspiratory (IPPB-I) in the correction of respiratory acidosis is well demonstrated in the following case report.

*Case 2.*—A sixty-two-year-old man with a history of chronic cough, bronchial asthma, shortness of breath and cyanosis was given oxygen by nasal catheter at ten liters per minute. Hypoventilation resulted and was followed shortly by coma. He was placed in a body respirator (Drinker type) for two hours and recovered. Several days later he was given oxygen again and this was followed once more by

TABLE IV. CASE OF RESPIRATORY ACIDOSIS INDUCED BY THE ADMINISTRATION OF 100 PER CENT OXYGEN AND TREATED WITH INTERMITTENT POSITIVE PRESSURE BREATHING—INSPIRATORY.†

| | Min. Vent. (L/min) | R.R. | Pulse | Arterial Blood * | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $pCO_2$ (mm Hg) | $pO_2$ (mm Hg) | Buf. Base (mEq/L) | $O_2$ Sat. (%) | Chloride (mEq/L) | pH |
| I (a) Control 8:45 A.M. | 5.500 | 16 | 88 | 69 | 40 | 63 | 74.58 | 92 | 7.40 |
| (b) 5% $CO_2$, 95% $O_2$ at 2L flow for 7 min | 5.300 | 17 | 80 | 63 | 62 | 61 | 89.48 | 92 | 7.40 |
| II (a) Control | | 17 | 82 | | | | | | |
| (b) 100% $O_2$ for 72 min. | 3.300 | 22 ** | 84 | 89 | 76 | 59 | 91.83 | 93 | 7.28 |
| III (a) Control | 3.300 | 22 | 84 | 89 | 76 | 59 | 91.83 | 93 | 7.28 |
| (b) I.P.P.B. Compr. Air 15 cm. $H_2O$, 2 hrs | 8.400 | 18 | 84 | 72 | 59 | 60 | 85.69 | | 7.35 |
| (c) At six hours | | 16 | 84 | 65 | 49 | 61 | 82.94 | 97 | 7.39 |

* Hematocrit — 40%
** Shallow

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respiratory depression and coma. On the following day, he was treated with an artificial pneumoperitoneum of 1,200 cc, supplemented by an additional 1,000 cc. This was followed by improvement of the patient's condition. He subsequently was studied in our laboratory in order to compare and evaluate the changes in ventilation with the findings in the arterial blood.

The results are summarized in Table IV and reveal: (1) a relative insensitivity to 5 per cent carbon dioxide; (2) the development of respiratory acidosis when breathing 100 per cent oxygen, as demonstrated by an increase of $pCO_2$ to 89 mm Hg and a decrease in pH to 7.28. These changes followed the marked decrease in minute ventilation (3.3 liters) and the development of ineffective ventilation (shallow respiration); and (3) the correction of this respiratory acidosis by the use of IPPB-I. Effective minute ventilation increased and this was followed by the return to a normal pH. The $pCO_2$ decreased toward its previous level, but remained above normal in this patient with chronic pulmonary disease. *The symptoms of respiratory acidosis disappeared when the pH became normal, even though the $pCO_2$ remained elevated.*

Barach and his associates[4] have recently developed a portable valve apparatus that may be used for intermittent positive pressure during inspiration or intermittent negative pressure during expiration, or both. The expiratory flow rates observed with the rapid exsufflation have far surpassed the capacity of the spontaneous cough of patients with pulmonary emphysema and bronchial asthma. The expiratory air blast carries a large volume of air, as well as secretions, out of the respiratory passageways at a time when the bronchi have been dilated by the previously ap-

plied inspiratory pressure. We are carrying on studies with this apparatus* in patients with chronic pulmonary emphysema. A rapid reduction in $pCO_2$ with improved ventilation should be observed in patients with the carbon dioxide intoxication syndrome.

## DISCUSSION

The term carbon dioxide intoxication syndrome has been coined by those who believe that the sequence of events constituting this syndrome is due to the accumulation of carbon dioxide. Others feel that the syndrome is caused by the change in blood pH and the development of uncompensated respiratory acidosis. Our views agree with the latter opinion. True as it may be that an accumulation of carbon dioxide (hypercapnia) will precede a shift in pH, however, until this breakdown in acid-base homeostasis occurs, none of the manifestations characterizing respiratory acidosis are seen.

Many of the patients with chronic pulmonary emphysema have a chronically elevated blood carbon dioxide level. They do not manifest the syndrome and they have a normal pH, unless further acute respiratory difficulty is added, making further compensation impossible and resulting in decrease of the blood pH. We administered 5 per cent carbon dioxide to a patient with chronic pulmonary emphysema, and this did not produce respiratory acidosis. Whether the disturbance starts following the acute relief of hypoxia by oxygen or with depressed alveolar ventilation due to morphine, the syndrome manifests itself when the pH falls below the normal range.

However, more important than the knowledge that the symptoms of the syndrome are caused by respiratory acidosis, is the realization that respiratory acidosis, from whatever cause, is basically due to *ineffective alveolar ventilation.* Therefore, the prevention as well as the treatment of respiratory acidosis requires the maintenance or restoration of effective alveolar ventilation.

## SUMMARY

(1) Respiratory acidosis, the actual disturbance of the so-called carbon dioxide intoxication syndrome, is discussed in this paper.

(2) Its manifestations range from weakness, headache, lassitude, and irritability to confusion, stupor, coma, hypoventilation, and death.

(3) Ineffective alveolar ventilation is the principal mechanism at fault in its development. This may be due to progressive chronic functional or organic lung disease, or is more often due to acute respiratory embarrassment secondary to drugs, acute relief of chronic hypoxia, involvement of the respiratory center, et cetera.

(4) Treatment of respiratory acidosis is discussed from three main aspects: Preventive, Etiologic, and Symptomatic.

(5) A case is presented which demonstrates the efficacy of Nalline and

*Exsufflator—manufactured by O. E. M. Corp., E. Norwalk, Conn.

another case which shows the efficacy of IPPB-I in maintaining effective ventilation with correction of respiratory acidosis.

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# HYPOALLERGIC PENICILLIN V
# (PYRIBENZAMINE - PENICILLIN)

## Comparison of Results and Final Conclusions From All Studies

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FOR THE past four years various antihistaminic drugs have been combined with Potassium Penicillin G in aqueous solution[10,11,12,13] in an effort to discover the mixture which would most nearly approach the ideal; i.e., resulting in no reaction due to acquired sensitivity to Penicillin. At first controls were used[10] but it was considered more advantageous to have more patients treated and dispense with controls as the desired result was a mixture resulting in no adverse reactions.

In the present series, as in the past, the Penicillin was prepared so that each milliliter of the saline diluent contained 100,000 units of potassium penicillin G* and 10 milligrams of Pyribenzamine® (Tripelennamine) hydrochloride (N, N-dimethyl-N'-benzyl-N'( $\alpha$ -pyridyl) - ethylene diamine). The Pyribenzamine** solution used contained 10 gms in 30 ml of saline in each rubber-capped vial which was sufficient for one liter of diluent for the penicillin.

During the eight months of these studies 1,237 patients received almost eight billion units of PBZ-Penicillin. The individual dose varied from 50,000 to 1,000,000 units given either as a single dose or as multiple doses every three, four, six, eight, twelve or twenty-four hours. The lowest total dose given any one patient was 100,000 units and the highest 37,000,000 units (over a period of forty-one days). The maximum dose in each twenty-four-hour period to one patient was 3,000,000 units. The average amount received for all patients was 6,000,000+ units. Over half of these patients had previously received Penicillin in some form.

All reactions occurring in patients receiving or having received Penicillin were personally inspected by the author. There were altogether only three during the entire eight months of the experiments.

*Case 1.*—The first patient was a seventy-two-year-old man with a diagnosis of pulmonary emphysema and fibrosis, arteriosclerotic heart disease and corpulmonale, decompensated. His medication consisted of digitalis, Mercuhydrin, Gantrisin, ammonium chloride and Pyribenzamine-penicillin 200,000 units every twelve hours. Due to a prostatic infection and atonic bladder an indwelling catheter was used. After one month on the named medications he developed a morbilliform eruption of the abdomen which was not pruritic and did not spread. The penicillin was stopped and the eruption cleared in three days without additional medication. He had had penicillin several times previously without reaction of any kind.

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Presented before the Ninth Annual Congress of the American College of Allergists, Chicago, Illinois, April 27, 1953.

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*The penicillin used was the product of Hayden, Pfizer or Squibb.

**Kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

TABLE I.

| Antihistamine | Strength in Diluent | No. of Patients | No. of Reactions | Per cent of Reactions |
|---|---|---|---|---|
| Decapryn® | 0.5% | 292 | 7 | 2.4 |
| Histadyl® | 1.0% | 1312 | 6 | 0.45 |
| Chlor-Trimeton® | 0.1% | 626 | 12 | 1.91 |
| Chlor-Trimeton | 0.2% | 470 | 3 | 0.64 |
| Chlor-Trimeton | 0.3% | 750 | 3 | 0.40 |
| Pyribenzamine® | 1.0% | 1237 | 3 | 0.24 |

*Case 2.*—The second reaction occurred in a fifty-eight-year-old man with a diagnosis of pneumonitis. PBZ-penicillin 200,000 units every four hours for four days and then every six hours for seven more days was given. Urticaria of the hands, feet and face developed. No response was noted on administering Pyribenzamine, Benadryl® or epinephrine for two days but complete clearing ensued on 20 mg of Cortone parenterally every six hours for five days. He claimed he had not received penicillin previously.

*Case 3.*—The third reaction developed in a sixty-seven-year-old man with a diagnosis of pneumonia. He was given 200,000 units of PBZ-penicillin every eight hours and Streptomycin one gram daily, both for twenty-one days at which time a generalized macular eruption occurred. Both medications were stopped and his skin cleared in five days without additional treatment. There was no history of previous administration of penicillin.

All three of these cases are considered to be reactions to penicillin although Case 1 is certainly not typical and the Gantrisin could have been equally responsible. In Case 3 we would have liked to try Streptomycin and Penicillin separately to determine if possible which was responsible but the pneumonia was cured and the patient refused.

As in our previous series the local anesthetic action of the added Pyribenzamine was noted. As much as six ml given at one injection produced no pain or residual tenderness. No side reactions, such as occur with oral antihistamines, were noted.

Therapeutic results were as good as with any other type of Penicillin. Frequent blood counts and chemistries, urinalyses, and other laboratory studies disclosed no adverse reactions due to the added Pyribenzamine.

The reaction rate using 10 mg of Pyribenzamine per 100,000 units of penicillin is thus 0.24 per cent (three reactions in 1,237 patients).

### COMPARATIVE RESULTS

In the course of these studies four different antihistaminic drugs have been used.[10,12,13] More would have been tried but Thephorin,® Perazil,® Diparalene,® Pyrrolazote,® and Bristamine® each formed a gummy insoluble mass when put in saline with the Penicillin. As far as possible each chemical group of antihistamines is represented. The Penicillin used was made by various manufacturers and no attempt was made to control the brand. Possibly some are more prone to cause reactions than others but this has not been noted in our control studies.

A comparison of our results is shown in Table I.

## DISCUSSION

The figures probably speak for themselves but there is no significant difference in the various antihistamines used if each is employed in its optimum concentration.

In comparing Penicillin with the newer antibiotics in various diseases, Penicillin is by far the drug of choice in most. Considering only skin reactions, here too Penicillin is more benign than the other antibiotics.[7] Reports of sensitivity to Aureomycin and Chloramphenicol were given in an earlier report[13] and to these many others may be added.[1,2,3]

Kalz and Prichard[5] state "In 53 per cent of all cases there were some side effects of Penicillin (procaine), not counting Jarisch-Hersheimer reactions and dermographia. There were cutaneous reactions in 41 per cent and respiratory and general reactions in 14 per cent."

Long[6] feels that the frequency of Penicillin reactions has risen to 10 to 15 per cent. Riley[8] in reviewing twenty-two reactions in his practice warns that the damage done may not be as transient as previously thought. One of his patients had erythema nodosum due to Penicillin which persisted for eight months.

The newer Penicillins apparently do not reduce the frequency or seriousness of reactions and crossed sensitivity has been demonstrated repeatedly.[4,9] Neo-penil has introduced another sensitizer along with the penicillin- iodine.

Skin testing for Penicillin sensitivity has been largely discarded as unreliable. It is impossible to predict how many patients will react regardless of past experience. Reactions are common from the first injection and thereafter sensitivity may increase, decrease or remain the same. What a chance we are taking when we inject procaine-penicillin knowing full well that it will remain in the tissues for months and supply enough by absorption to continue for that long any reactions which might arise.

If numbers mean anything our experiences in over 5,000 patients given Penicillin with antihistamine added should convince the most skeptical that the rate of reaction thus obtained is far below that resulting from the same Penicillin without the antihistamine or from other Penicillin combinations.

## SUMMARY AND CONCLUSIONS

Pyribenzamine in a concentration of one per cent was added to the diluent for Potassium Penicillin G. This combination when administered to 1,237 patients produced only three reactions or 0.24 per cent. No adverse reactions were produced and the therapeutic efficiency of the Penicillin was not lessened.

In comparing the various antihistaminic drugs combined with Penicillin it is noted that each probably has an optimum concentration to produce the fewest reactions. The per cent of patients reacting to this Penicillin

combination is far below the rates reported to plain crystalline Penicillin or other Penicillin combinations.

In closing, it is entirely fitting to quote in full the last paragraph in the conclusions of Smith and Walker in their book, *Penicillin Decade*—"By desensitization and the considered use of antihistaminics or other detoxifying agents, surely the great number of reactions recorded in these pages need not be found in the literature of Penicillin's second decade. While the actual toxicity of Penicillin is almost negligible, its ability to sensitize and to cause serious and even fatal accidents should not be minimized. A grave responsibility rests upon the shoulders of the physician for its wise application in clinical practice."[14]

ACKNOWLEDGMENT

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# Editorial

*The opinions expressed by the writers of editorials in the* ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

## QUANTITATIVE ASPECTS OF IMMUNE THERAPY OF ATOPIC ALLERGIC DISORDERS

It is a matter of clinical judgment that the majority of our allergic patients, subjected to "desensitizing" treatment get well. In the absence of any objective methods of immunologic assay, there are, therefore, many shades of opinion about the techniques of treatment for instance concerning the optimal quantity of extract for "desensitization" in patients sensitive to pollen or house dust.

For an approach to this problem, it may be of interest if we compare antiallergic desensitization procedures with antimicrobial immunization. Such comparisons are especially helpful when we realize that our allergens are true antigens, as proved by the appearance of precipitating and complement-fixing antibodies.

The quantity of active material actually present in any therapeutic extract cannot be accurately weighed or measured at the present time. We do know, however, that it is contained in the protein nitrogen portion, of which an appreciable part is probably effectively antigenic. In terms of the commonly used nitrogen unit of 0.00001 mg N, 1000 U of pollen extract contain 0.01 mg N, or about 0.06 mg of protein. Taking it the other way around, for an average patient weighing 70 kg, a dose of 1000 U of extract, would represent 0.0008 mg of antigen per kg body weight, or a measurable fraction thereof, say in the order of magnitude of 0.0001 mg.

How does this quantity compare with that of a microbial antigen capable of evoking a significant and measurable antibody response? Although there are few quantitative results available to us, we do possess some relevant data.

An injection of 10 to 50 Lf of diphtherial toxoid will, in man, stimulate antitoxin production. Six milligrams of the pure protein of this toxoid solution, representing 1 mg of nitrogen, contains approximately 2,500 Lf. Thus, 0.024 to 0.12 mg/N, or 0.0004 to 0.002 mg toxoid/kg body weight represents the amount needed to evoke antitoxin responses in the majority of subjects. With pneumococcal carbohydrates it was demonstrated by Heidelberger and his associates that antibody response may be obtained with injections of 0.03 to 0.05 mg antigen, which would correspond with 0.0004 to 0.0007 mg antigen/kg body weight.

There is, moreover, the important difference between data obtained from immunization procedures with diphtheria toxoid and pneumococcal poly-

saccharides, and the use of the antigens in pollen extracts. The former are the result of single doses given as protection against infection. We are comparing these with the multiple doses of pollen extract, usually given in the therapy of allergies. Experimental data have demonstrated that injected antigens may be retained within the cells for extended periods of time. Repeated injections of pollen extract can, therefore, be expected to produce cumulative effects, both by retention and by "booster" effects. In actuality, therefore, the lower limits of effective dosage is probably much smaller than those exemplified above.

Reinforcement of this conclusion may be seen in the work of Kuhn and Pappenheimer, who observed the development of dermal reactivity of the wheal and flare type in a large percentage of their subjects given booster doses of diphtheria toxoid. The capacity of acquiring such sensitivity could be correlated with the presence of personal or familial allergy of the atopic type. Allergists have frequently noted the ease with which atopic individuals acquire new sensitivities.

For obvious reasons human subjects cannot be subjected to the type of experiment which would demonstrate the minimal amount of an antigen needed to sensitize. But from the experience in animals we can conclude that it is probably quite small, and may be minute in those constitutionally inclined towards sensitization. That the size of such doses plays some part in sensitization procedures can be concluded also from the experience in serum sickness. The latter is usually produced by large doses of antigen but will result only in exceptional cases following the injection of small amounts of serum.

In man, it remains a moot question, whether large doses of antigen may be less effective in stimulating antibody response than smaller ones. Experience in animals certainly supports the possibility of such seemingly paradoxical effects. About ten years ago, Felton reported data which tend to show that large doses of pneumococcal carbohydrate may permanently paralyze the ability of the mouse to respond to the particular antigen.

In recent years, numerous data have been reported (several in the pages of this journal) which tend to show that in the immunizing therapy of atopic allergies smaller doses than used in the past may be preferable not only from the viewpoint of greater safety but also of greater therapeutic effect. One would be inclined to think that considerations like those presented here fit well with such contentions.

## PARADOXICAL THERAPEUTICS

The cyanotic, breathless, gasping, hypoxic patient may suffer harm or even die, when the therapeutic agents he needs most, oxygen or sedative drugs, are improperly administered alone or in combination—a real example of "paradoxical therapeutics."† These are generally the first medicaments to be administered to such patients; usually the color improves

promptly and the dyspnea lessens, but central nervous system symptoms may develop as the therapy is continued.

Among physicians caring for patients with chronic pulmonary emphysema, there has been an increasing awareness of a clinical picture comprising mental changes, due to profound disturbances of the acid-base balance, which may progress even to coma and death: the so-called "carbon-dioxide intoxication syndrome." Segal and his associates give evidence that this syndrome is not due to the accumulation of carbon dioxide in the arterial blood, as long as the homeostatic mechanism regulating the acid-base balance remains intact. A break in this homeostatic mechanism may be followed by a decrease of the arterial pH and the development of uncompensated respiratory acidosis. The authors clearly describe the clinical manifestations and their physiologic basis as noted in the patient with respiratory acidosis. They stress the importance of the compensatory attempts of the hyperventilating patient to maintain a normal carbon dioxide level by more effective alveolar ventilation. Ineffective alveolar ventilation appears to be the principal mechanism at fault in the development of respiratory acidosis, from whatever cause.

It should be kept in mind that although respiratory acidosis is seen most commonly in chronic organic pulmonary disease, especially in the course of chronic pulmonary emphysema, it may occur in the course of chronic functional pulmonary disease, such as kyphoscoliosis or progressive restrictive pachypleuritis and in the acute respiratory insufficiency observed in neuromuscular involvement of the respiratory center, drug intoxication, or asphyxia. Fortunately it is not usually encountered in the course of the acute attack of bronchial asthma or in status asthmaticus, unless the patient has underlying chronic pulmonary emphysema. Accurate diagnosis can be made by determining the carbon dioxide content and pH of arterial blood or of (anaerobically obtained) venous blood.

Treatment should be first of all *preventive:* realizing the conditions in which this syndrome is apt to occur, one should avoid high concentrations of oxygen and respiratory depression drugs. When oxygen must be given, it should be used in very low concentrations and increased gradually every one or two days. Treatment should be directed at the *etiologic* cause: Nalline® for opiate depression; Picrotoxin® for barbiturate depression; and bronchoscopy or tracheotomy for relief of airway obstruction. Finally, treatment must also be *symptomatic:* pressure breathing or emergency pneumoperitoneum therapy for ineffective alveolar ventilation, and a program of guided oxygen therapy for the relief of the hypoxia and cyanosis.

One should be alert to the "carbon dioxide intoxication syndrome" of chronic pulmonary emphysema accompanied by chronic bronchial asthma.

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†Segal, M. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema. Physiopathology and Treatment. Grune and Stratton, Inc., New York, 1953.

# Progress in Allergy

## PEDIATRIC ALLERGY

### A Critical Review

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During the past year, a large volume of literature on pediatric allergy has accumulated. The following review will discuss not only the papers which have been published referring directly to allergy in children, but also will include discussions of allied subjects, even though the patients under discussion were both children and adults, or in some cases, all adults.

#### DERMATOLOGIC ALLERGY

Brain[12] has published a general discussion of the subject of eczema including pathology, etiology, clinical types and treatment, and this is not suitable for review. The author includes many of his own impressions. For example, skin testing is of little value in eczema, and milk allergens are of little importance in the causation of eczema in infancy.

While there are allergists who agree with these two impressions, others believe that skin testing is of considerable value in eczema and that milk allergens are often of importance in the etiology of the disease.

Rostenberg et al[66] made an investigation of the sensitivity to bacterial allergens as a cause of atopic dermatitis. They cultured all organisms aerobically and anaerobically found on the diseased skin, normal skin, and nose and throat of some atopic patients. Vaccines from each strain grown were tested on the patients. Immediate positive reactions obtained with unground and ground vaccines were essentially the same, but the latter gave more delayed positive reactions. Control tests on non-atopic individuals did not give results different from atopic individuals. The author's results did not support the bacteriologic etiology of atopic dermatitis.

Many attempts similar to this have been made to determine the importance of bacteria as a cause of atopic dermatitis but because of secondary contamination which almost inevitably results in any case of prolonged dermatitis and because of the difficulty of evaluating skin tests performed with bacterial extracts, this problem is one which is very difficult to solve. It is possible that an entirely new approach will be necessary if it is ever to be solved.

Baird et al[5] discussed the successful treatment of eczema of the ear canal. They believe that eczema of the ear canal is fundamentally a sensitivity reaction of the skin, frequently due to products of bacteria. They believe that the bacteria may be located in such foci as the sinuses, tooth

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roots, or throat. Of their ten cases treated with bacterial vaccines with good results only one was a child, aged fourteen years.

While this is a plausible type of therapy in those cases which are due to sensitivity to bacteria, there are a great many cases of eczema of the ear canal due to other allergens including foods and inhalants and it would not be expected that this form of therapy would be successful in these types.

Baer et al[4] did experiments on the differential cell counts in the blister fluid of allergic eczematous and irritant bullous lesions. They examined the blister fluids of allergic eczematous reactions, of primary irritant reactions produced in the grossly unaffected skin of non-eczematous dermatoses, and of primary irritant reactions on the normal appearing skin of patients with allergic eczematous contact type dermatitis. The allergic eczematous contact-type reaction showed a preponderance of mononuclear cells in thirteen of seventeen counts. Primary irritant reactions showed a preponderance of polymorphonuclear cells in forty-six of fifty-seven counts. The differences in the cellular content appeared to occur with sufficient regularity to suggest that differential counts are helpful in the diagnosis of allergic eczematous lesions and of primary irritant, vesicular bullous lesions. However, there were a sufficient number of exceptions to this rule to preclude reliance on the cell count as a pathognomonic finding of absolute value in differential diagnosis.

Experiments similar to this have been tried many times and the authors point out the fallacy of relying on this in differential diagnosis.

Snyder[73] reports the use of terramycin in one child with eczema vaccinatum. Terramycin was employed successfully in the treatment and there was a remarkable improvement in symptoms with clearing up of lesions.

This one case does not give any evidence that terramycin is specific in the therapy of this condition, because it is well known that most of these patients get better anyway and are helped by the other antibiotics since there is almost always a secondary infection complicating the disease.

Inman et al[40] studied the use of antihistamines in non-urticarial dermatoses with the use of antihistamine iontophoresis. They studied twenty patients, only one of whom was a child and all had dermatitis but all were not suffering from allergic dermatitis. The method was free from toxic reactions and for localized areas of chronic dermatitis they thought it had useful, though limited, value.

Two papers have appeared on allergy to insects. Rockwell[63] studied mosquito bite reactions. Using sterile extracts of different sections of mosquitoes, he demonstrated that various portions of the mosquito produced similar reactions in sensitive individuals. He found the small mosquito bite reactions can result from irritation alone but that there are three clinical types of allergic reactions which follow mosquito bites: (1) urticarial (2) tuberculin (3) eczematous. Hyposensitization was attempted in three patients and in all cases the reaction became less severe but the patients continued to develop late papules following mosquito bites. The authors feel that aqueous mosquito extracts are toxic in high concentration but the weaker concentrations are of value in the diagnosis and treatment of mosquito bite reactions. Although there are few patients who show severe reactions to mosquito bites, hyposensitization would be worth while in those in whom reactions are very severe.

Shaffer et al[71] put forth evidence that papular urticaria is related to insect allergy. They put forward the following evidence: *Clinical evidence*

—The initial lesions have the appearance of insect bites. *Epidemiologic evidence*—The disease appears almost exclusively in the warm weather months and it reaches its peak frequently in midsummer. A careful history in many cases of papular urticaria will reveal exposure to biting insects or the presence of sources of these insects. In addition papular urticaria often has its onset after the patient moves from one geographic location to the other. *Allergic evidence*—They tested thirty patients with papular urticaria and 124 controls of corresponding age group with both flea and cimex antigens. Reactions to flea or cimex antigen or both were obtained in 77 per cent. Of the 124 control subjects, only two reacted positively to cimex antigen. *Histologic evidence*—Other workers have found a striking similarity histologically between insect bites and the lesions of papular urticaria and positive skin tests to insect antigens. *Therapeutic evidence*—Other authors have reported the cure of papular urticaria by the use of DDT on the patient and in the household.

The authors feel that many cases of papular urticaria represent a phase in the developmental cycle of the individual to insect allergy. In the normal individual, the tuberculin type of sensitivity is transient and/or ill developed but in papular urticaria, this phase is prolonged and severe and dominates the clinical picture. This concept of papular urticaria fits in with the feelings of many allergists and in any case of papular urticaria it would certainly be worthwhile trying insect control with the use of DDT.

Two papers have appeared on poison ivy dermatitis. Barefoot[7] discusses the complications of poison ivy dermatitis. These complications may be systemic or therapeutic and may be in the skin and/or the kidneys. The most common complication in the skin is secondary infection. In rare instances, the acute dermatitis is followed by a chronic eczema. The author has never encountered a patient with recognized renal complications but cases are reported in the literature, some manifested by nephrotic syndrome and some by the clinical picture of acute glomerulonephritis. While Rhus extracts may be used in therapy, the extracts should never be injected during the acute blistering phase of the disease. The author has seen one patient with what was apparently a toxic psychosis from injections of Rhus extracts; this was in a fifteen-year-old girl.

Besser et al[10] discussed the peroral prophylaxis of poison ivy dermatitis. Their report concerns the prophylactic use of capsules containing the seeds of poison ivy in 155 persons exposed to poison ivy at camp. Children between forty-five and seventy-five pounds were given capsules containing one milligram of the poison ivy seeds, those from seventy-five to 110 pounds, capsules containing 3 milligrams and those over 110 pounds, capsules containing 5 milligrams. The prescribed dose for all groups was one capsule daily, one-half hour before breakfast. All started to take the capsules about two weeks before going to camp and all were instructed to continue taking one capsule every morning while at camp. The children were accepted for this treatment only if they had a past medical history of poison ivy and showed a positive patch test with an acetone solution of the oleoresin of poison ivy and a negative patch test control. In the first group there were fifty-two individuals consisting of forty-eight children and four adults; of these forty-four were reported as remaining free of dermatitis and eight had mild eruptions which were milder than they had suffered previously and did not curtail their activities. Of the second group of 103 children, follow-up could be done on only thirty-seven. Of these, twenty-one had no eruption at all, six had very mild eruptions and

seven had some eruption but milder than in previous years. Three had their usual attacks. The authors conclude that these results are very encouraging, the administration is simple and the untoward side-effects are very infrequent and extremely mild in nature.

This study suggests an easy way for preventing or minimizing symptoms of poison ivy in susceptible individuals. However, the results of the study are rather inconclusive because it has not been possible to ascertain the amount of exposure that the children had at camp; the length of time the children were at camp was also very variable and in no case was it certain how regularly the medication was being given.

### RESPIRATORY ALLERGY

Two papers have appeared giving long-term followups on children with asthma. The first, by Rackemann et al[55] was a twenty-year follow-up of 688 patients with asthma. These consisted of 449 children with asthma who were first seen before the age of thirteen years and another 239 patients whose asthma had begun before thirteen years but who were not seen by the authors until after thirteen years of age. Each patient was followed by letter or other means after an interval of about twenty years after the first visit. The majority were private patients. Of the 449 children who were first seen before the age of thirteen years, 114 suffered from asthma due primarily to contact with animals. These patients in general did fairly well because of the ability to recognize and remove the exciting factor. In thirty-six patients, foods were the primary cause of asthma. Egg and fish were the most common foods implicated as the most important cause of the asthma. The food patients lost their clinical sensitivity entirely in high proportion, 44.4 per cent. In only twenty-one cases was the asthma primarily due to pollens, showing that this is relatively an uncommon cause of asthma in childhood. Most of these patients retained their sensitivity. One hundred and ninety-nine patients were described as mixed or unidentified in type although they had positive skin tests and were considered to have extrinsic asthma. In seventy-nine patients, the skin tests were all negative. Of these 449 patients, 30.7 per cent were entirely relieved at the time of follow-up; the average age of cessation of asthma had been 14.7 years with a range of five to thirty years. If they avoided the things to which they were sensitive 19.3 per cent were well but were still sensitive to the exciting allergens; 21.4 per cent had little or no asthma but had developed other allergies, chiefly hay fever. This makes a total of 71.4 per cent who had done very well, being free or almost free from asthma; 26 per cent were still having trouble at the age of fifteen years but in only 10.9 per cent was this difficulty serious. In the group there had been eleven deaths but only four of these were due to asthma. The group of 239 patients who were not seen until after the age of thirteen years was a more selected group, since it consisted of patients with a more persistent form of asthma. Only a little over half of these patients did well and 27.6 per cent were still having serious trouble. Six of these patients had died of their asthma. A suppplementary report of eighty-six children with hay fever is included. These had been seen before the age of thirteen years and in only two of these was there a cure. The other eighty-four still had their hay fever. The author points out that sensitivities to pollens are evidently different from the sensitivities to animals or foods and inhalants. A possible reason for this may be that the pollens return each year and the patient cannot escape from them as he can escape

from the other inhalants and the foods. The author feels that part of the reason is that a pollen is a good allergen in the sense that it induces sensitiveness easily, whereas on the other hand it is not a good antigen for producing antibodies.

The figures given in this paper are very interesting since they show that a large proportion of asthmatic children can be expected to do well. Since many of these patients were investigated and treated years ago before our present means of therapy were available, it would be interesting to compare this series with a series, all of whom were treated by the modern methods of therapy.

The second study of a long-term followup on bronchial asthma in children is by Unger et al.[75] These authors report a follow-up study on 306 asthmatic children in whom symptoms began before the age of thirteen years. These patients had been seen over a thirty-year period but no patient is included in the study unless at least one year had elapsed since treatment was started. All the patients had been receiving treatment. They were all private patients. The follow-up was conducted by questionnaire in the case of those patients who could not be seen personally. In the 306 asthmatic children, both paroxysmal and chronic, complete relief occurred in 32 per cent, marked and moderate relief in another 60 per cent, no improvement in another 5 per cent, and death in 2½ per cent. The results of treatment did not seem to be related to the age of onset of the asthma. Comparison of these figures with a previous report on 459 cases in both adults and children, showed that the prognosis in children is obviously much better than that in adults and the outlook for those with paroxysmal asthma is much better than in the chronic cases. The duration of paroxysmal asthma does not seem to alter the prognosis in children but early onset of chronic asthma is a distinct handicap in both children and adults.

The cases were further analyzed according to the type of primary allergen. The best treatment results were obtained in the pollen sensitive group, forty-four of seventy-nine of this group became asthma free, chiefly by the use of injections of the specific pollen extracts, failure occurred in only three of this group. The results were also good in those patients whose asthma was primarily due to fungus. Foods were the prime cause of asthma in only about 10 per cent of cases. Negative skin tests occurred in only 1 per cent, probably because the cases were very completely tested. The authors believe that while colds and other infections are important factors in bronchial asthma in children, their importance diminishes when the causative inhalant or food allergens are discovered and minimized or removed. When other allergies in these patients were studied, it was found that about 40 per cent of all cases of hay fever, sooner or later developed bronchial asthma. In the author's experience, the perennial type of rhinitis is even more likely to end up in asthma. The authors also discuss the diagnosis of bronchial asthma, the prevention of asthma and the treatment of the acute attack both specific and symptomatic. They feel that their own results reported can be improved upon because we can go a long way in minimizing and perhaps preventing asthma. Progress will depend on further education of the medical profession and of the laity.

This is another excellent long term follow-up of children with asthma. The author's figure of approximately 90 per cent good results in treatment agrees with those of other authors. The differences observed in the children whose asthma was due chiefly to pollens is very interesting, Rackemann having found that they did poorly and Unger having found that they did best of any of the groups studied.

Fuller[30] reports a series of 209 asthmatic children attending an Allergy Clinic in England over a four-year period. Positive skin reactions were obtained in only 51 per cent. By far the largest proportion of positive reactions was associated with the inhalant groups, particularly feathers, down, horse hair and house dust. Only sixteen children were sensitive to the pollen group and most of these to grass pollens. Ragweed sensitivity was not observed. Clinical or radiologic evidence of pulmonary disease other than emphysema was obtained in twenty-one patients, including such conditions as bronchiectasis and tuberculosis. In twenty-four children the asthma coincided with or followed immediately after an attack of whooping cough. The standard method of prophylaxis against an attack was the regular administration of phenobarbital but the children who were constantly wheezing received small doses of ephedrine along with phenobarbital. Children whose skin tests showed specific sensitivity were given courses of desensitizing injections if they were over five years of age. In some cases, feathers, and pillows and so on were removed from the bed or from the immediate proximity of the child, but only in the highly allergic was any change made in the more distant furniture of the room because it was felt undesirable to give the bedroom an abnormal appearance, in case the child's feeling of invalidism should be increased. Tonsils and adenoids were removed in most of the patients. Forty children had antrum washouts and eight had other intranasal operations. Many of the children were given breathing exercises. Of the 179 children followed for at least six months, ninety had no attacks during the six months prior to the time of collection of the data and seventy-seven had markedly fewer attacks. In the whole series there were forty-four children who had been free of attacks for more than one year.

This study shows many differences from similar studies on this continent. The 51 per cent positive reactions is exceedingly low. The author does not state whether the testing was done by the scratch or the intradermal method but the low incidence of positive reactions suggests that only the scratch method was used as one would expect to find at least 90 per cent of the children to have positive reactions. The observation on the lack of ragweed sensitivity is not surprising, since ragweed is not widespread in Europe the way it is on this continent. No explanation is given as to why it was only children over five years of age who were given courses of desensitizing injections. The author's attitude towards elimination of offending allergens, only in the bedroom and not other rooms, is not commonly accepted in this continent.

Unger and Unger[76] give a very comprehensive review of the subject of the treatment of bronchial asthma.

Nove[53] reports a clinical study of the relation between the bony framework of the skull and respiratory function. The author's method consisted of making a splint to restore the mouth to normal shape so that over a period of time there would be a reconstruction from a faulty structure of the face to one that is so balanced as to restore normal breathing.

This is a most original approach to the problem of asthma in children. While one must agree that there could be cases where deformity of the face caused abnormality of movements of the muscles of respiration and of accessory respiration, it is very difficult to see how this approach could in any way influence the presence of antibodies in the bronchial and bronchiolar musculature, or in any way affect the pathology of the lower respiratory tract. Considering the large number of children who suffer from

asthma, it is difficult to believe that there are any more than a rare few who could respond to this form of therapy.

Baird[6] reports on the effects of bacterial antigen plus antibody on bronchial asthma. Based on twenty-five years' experience, the author feels that increasing doses of mixed bacterial antigen plus antibody will give some relief in nearly all cases of bronchial asthma and when bacteria are more obviously concerned usually gives such complete control that no other complicated study or treatment is required.

This is a departure from the accepted methods of treatment of bronchial asthma. While it could be expected to give good results in those patients whose asthma is due to sensitivity to bacteria, it is difficult to see how it could be more satisfactory than conventional methods in the treatment of those patients who have been proved to be sensitive to foods, inhalants and pollens.

Mueller and Flake[52] report on the radiation of the nasopharynx in children with infectious asthma. They report forty-one children so treated and results were observed for periods of six months to four years with 85 per cent of the patients followed for two years or more. The patients were carefully selected by the allergists and the otolaryngologists. Of the entire group of forty-one patients, eleven or 21 per cent obtained complete relief for a period of two to four years. Seventeen patients, or 41 per cent, obtained excellent results for periods of eighteen months to four years. Five patients or 12 per cent, obtained only fair results and in eight patients, or 20 per cent, results were unsatisfactory.

This paper draws attention to another ancillary method of treatment for the allergic child. The authors do not pretend that it is the prime treatment for asthma. They point out that their group is a select group of patients who had done poorly under all types of treatment and it should be emphasized that this method of therapy should be a secondary one to the usual allergic investigation and treatment by hyposensitization.

Schiller and Lowell[68] give a report on the inhalation test as a diagnostic procedure. Induced asthmatic attacks can be readily detected by the attending decrease in vital capacity and slowing in the expiratory rate and in many subjects these changes follow the inhalation of aerosolized allergenic extracts. The authors describe the inhalation method as a diagnostic procedure in a group of seventy-five asthmatic patients who ranged in age from six to sixty-two years with mild or severe asthma, but at the time of study they were free or almost free of asthma. They were studied from the point of view of history, skin reactions by the intracutaneous method and inhalation tests with pollen extracts of birch, oak, timothy, and ragweed; extracts of alternaria and hormodendron and house dust extract. The incidence of skin reactions was much greater than that of pulmonary reactions and the occurrence of a pulmonary reaction on exposure to an aerosolized allergen could not be satisfactorily predicted on the basis of skin tests. On the other hand they failed to produce pulmonary reactions with allergens which did not give skin reactions.

This paper draws attention to a procedure which is valuable in the diagnosis of the etiologic factors in asthma and points out that all positive skin tests are not necessarily of clinical significance. Unfortunately it is a laborious procedure for the clinical study of a patient, but is a very useful tool in the study of specific factors such as the etiologic relationship in asthma of house dust and ragweed in a given group of patients. The weakness of this study is that unless these authors used all the allergens the

patient was sensitive to, their evaluation of clinical results could not be properly assayed.

Bullen[14] reports on the correlation of clinical and autopsy findings in 176 cases of asthma. The material in the study was obtained from the examination of the records of 176 hospitalized patients who died. The majority of cases studied were adults and the authors do not state exactly how many of them had their onset of asthma in childhood. However, there were thirteen patients whose asthma had begun in the first five years of life. The authors point out that there is general agreement of the presence of a thick, tenacious material in the lumina of the tubes and edema and swelling of the mucosa and sub-mucosa as important causes of bronchial and bronchiolar obstruction, but that there is controversy as to whether constriction of the tubes by the circular muscles of the bronchi contributes to the reduction of the size of the air passages. They quote two autopsies, one in a child and one in an adult, in both of whom the bronchi were occluded by mucous plugs. The amount of mucoid secretion in the bronchi of the patients who died in asthmatic attacks varied from quantities which completely plugged even some of the large bronchi, to almost none in a few cases. It was also noted that some of the individuals who died of intercurrent disease or injury with no asthma at the time had larger quantities of this secretion than is commonly found in bronchi in non-asthmatics. All the patients did not have allergy studies because many were not seen until the terminal illness but of those who died of asthma in childhood or in early adult life, specific sensitivity to the common allergens was much less common than it is in the asthmatic seen in routine practice. Bronchiectasis was found in only nine cases. In slightly more than half the patients, death occurred within ten years after the onset of asthma and in one-fifth, within five years. Most of these cases were individuals whose asthma began after the age of forty but six patients died under five years of age. Of these six individuals none showed specific sensitivities to foods or inhalants. The authors attempt to answer the question as to whether or not asthma damages the heart and conclude that, if marked emphysema develops in the asthmatic, heart injury is likely to result.

The presence of eosinophilia was unexpectedly low in these patients, in about one-third no eosinophils were noted in the routine blood counts, but on the other extreme, counts of 20-40 per cent were present in a few cases. In only about one-fourth of the reported cases of death from asthma was there evidence that the asthma was the result of sensitivity to ingestants or inhalants. This gives the impression that intrinsic or bacterial asthma presents a greater hazard to life.

This paper stresses the pathologic findings in bronchial asthma, namely mucus in the bronchi and bronchioles, edema of the mucous membrane of these structures as well as the possibility of constriction due to muscle spasm. The figures also confirm the general impression that patients who, under investigation, show specific sensitivities which can be treated, do much better than those in whom specific sensitivities cannot be determined. The fact that in so many of these patients the asthma had dated from childhood emphasizes the importance of treating asthma in childhood and attempting to prevent the disease continuing into adult life.

Royle[67] reviews 200 cases of asthma according to their x-ray appearance. There were 100 children aged fourteen months to twelve years. In the children the average duration of the disease was three years, ten months and in the adults eleven years, ten months. X-rays of the sinuses were done in all cases. In the children 90 per cent showed minor changes and 43 per

cent showed marked changes. In the adults only 18 per cent showed minor changes and 36 per cent marked changes. Chest x-rays were done in all cases studied. Of the 100 children, fifty-seven showed no abnormality, twenty-two had emphysema only, six had emphysema plus increased hilar shadows, eleven had increased hilar shadows alone and four had segmental collapse. The same figures for the adults respectively were thirty, thirty-five, eleven, fourteen, and four, there being six with other important abnormalities. The authors point out that by repeat physical and x-ray examination it is possible to tell the difference between irreversible, chronic hypertrophic, pulmonary emphysema and pulmonary distension due to an asthmatic attack. In both children and adults the average duration of the disease was longer in those with emphysema. He emphasizes the importance of segmental collapse which was seen in eight patients, four children and four adults. In some of these, re-expansion was rapid, in others it was a slow process. He feels that the collapse is due presumably to the blocking of small or large tubes by mucous plugs and is commoner in asthma than is generally realized although all degrees of it up to massive collapse of the whole lung have been described. He concludes that the chest x-ray in uncomplicated asthma is normal, but that a great deal of help can be obtained from radiography in the diagnosis of complications and in the discovery of co-incident conditions.

This paper is important for several reasons. In the first place it stresses the importance of x-rays of the chest and sinuses in the allergic work-up of every patient with asthma, and stresses, by implication, that if sinusitis is present, it must also be treated if a good result is to be obtained. It also stresses the fact that other diseases may be present in the asthmatic, since in some cases, the increased hilar shadows may be due to such conditions as tuberculosis. It also points out the frequency with which segmental collapse occurs and this is important because if re-expansion is to be obtained, treatment should be started early. The best method of producing re-expansion is to give the patient an emetic dose of syrup of ipecac which causes vomiting which in turn helps to expel mucous plugs from the lower bronchi. By this method, there can be very rapid re-expansion of the atelectatic portion, if the emesis is done early. This use of ipecac has been emphasized in several papers by Ratner who believes this to be the most important therapeutic adjuvant in the treatment of status asthmaticus.

Overholt et al[54] discuss hidden or unsuspected bronchiectasis in the asthmatic patient. They point out that chronic irritation causes muscle spasm and that prolonged muscle spasm augments chronic irritation and that the classical symptoms of bronchiectasis, cough, hemoptysis, and the production of purulent sputum are irritative factors that can, and frequently do, produce a bronchial spasm. They point out that bronchiectasis occurs fairly frequently in asthmatic children and that hemoptysis, purulent sputum, repeated pulmonary infections and localized physical findings over the lung fields strongly suggest the presence of bronchiectasis, especially in asthmatic patients. They report seventy-six patients with severe bronchial asthma who had been classified as medical failures since they had not responded favorably to conservative treatment. Bronchography was done on seventy-five patients and revealed bronchiectasis in twenty-seven of whom thirteen had the disease bilaterally. Of these twenty-seven, twenty-six patients were treated operatively and twenty of them were greatly improved in health. Only seven required broncho-dilative drugs. They conclude that bronchiectasis, hidden and unsuspected, is often present in the asthmatic patient and removal of the abnormal segments can bring per-

manent relief. Although all the case reports in this paper are adults, the same problem is present in asthma in children and the question of bronchiectasis must be seriously considered in every asthmatic child.

Rosen[64] reports on twenty patients with bronchial asthma whose attacks usually followed an upper respiratory infection or in whom the attack occurred concurrently with an upper respiratory infection. The group included five children. All patients were symptom-free and appeared physically normal between their attacks of asthma. In only three were the upper respiratory infections regarded as the sole cause of the asthma. Each patient was given terramycin capsules with instructions to take two capsules at the onset of wheezing and then one capsule three times a day thereafter. Of the twenty patients, thirteen were relieved of their attacks within forty-eight hours, a few within twenty-four hours. Most of the patients had noticed that attacks previously would last four to seven days. Four patients were not helped by the terramycin, three patients were relieved of their attacks within four days. The authors believe that terramycin is indicated to be of value in the treatment of patients suffering from infectious asthma.

It is very common, especially in children, for attacks of asthma to be initiated by an upper respiratory infection. Some regard this is a trigger mechanism, some as the cause of the attack. In such cases it is to be expected that an antibiotic, whether terramycin or some other, would be helpful in relieving the attack inasmuch as it clears the upper respiratory infection which helped to initiate the attack. However, these drugs should not be used indiscriminately in the treatment of every attack of asthma because of the danger of drug sensitivity.

Ratner et al[56] described the allergic dermal-respiratory syndrome in children, which is defined as a symptom complex, in which both dermal and respiratory manifestations of allergy occur in the same patient either synchronously or at different periods. In a study of 750 allergic children, they found that 35 per cent of the cases fell into the category of the dermal-respiratory syndrome, and that 59 per cent of those children who had had allergic eczema at the time they were seen, or previously, later had respiratory allergy. The authors describe three stages in the evolution of this syndrome. Stage 1: Dermal manifestations are present, respiratory symptoms are absent and there are negative skin reactions to inhalants, but may be positive reactions to foods. This stage is present chiefly in infants. Stage 2A: There are dermal manifestations. There are no respiratory symptoms but positive skin tests to inhalants have now developed. Stage 2B: There are dermal and respiratory manifestations but negative skin reactions to inhalants. Stage 3: We have the fully blown syndrome with dermal and respiratory symptoms and positive skin reactions to inhalants. Stage 3 occurs almost entirely in older children. The authors conclude that eczema in infancy or childhood should not be regarded solely as a dermatologic condition, but that every case of dermal allergy should be viewed as a potential case of asthma or hay fever. The need for adequate and appropriate treatment for inhalant sensitivity is stressed and the hope is that by treating such cases from a broad, general and allergic standpoint, development of more serious allergic manifestations, such as asthma may be prevented. This concept is in keeping with the general attitude in pediatrics at the present time, mainly, that prevention is more important than treatment of the preventable disease after it has developed.

Fontana[26] reviews the recent literature on asthma in children. He stresses the importance of early recognition of allergic symptoms in an infant, prior

to the onset of asthma, as proper treatment will lessen the possibility of a defect in growth and development and may prevent more serious allergic manifestations from developing. The discussion is a general one and will not be further summarized.

Two rather extensive reviews on respiratory allergy have also been published in the past year. The first by Segal et al[70] is a review of the literature on bronchial asthma. It has 146 references. The second by Kaplan et al[43] is a review of literature for 1950 on hay fever. It has 245 references.

### ACTH AND CORTISONE

Bowman et al[11] studied the immediate effect of a single dose of ACTH upon the skin reactions to testing with atopens and histamine in atopic individuals who at the time of the experiment were well and symptom free. They succeeded in demonstrating in a majority of subjects, a slight but definitely depressive effect of the hormone upon the atopic cutaneous skin reactions.

It is generally agreed that any depressing effect that ACTH may have on positive skin reactions is so slight that for practical purposes it is not a contra-indication to skin testing, if the patient is on either ACTH or Cortisone.

Glaser[32] reports a study on five infants and children varying in ages from six months to fourteen years who were treated for their eczema with ACTH or Cortisone. Good temporary results were obtained in all cases; the restitution of the skin was in no instance completely to normal, but in every instance was satisfactory from the standpoint of itching and of the appearance of the patient.

The evidence is that both ACTH and Cortisone produce the same therapeutic effects as far as eczema is concerned. Cortisone should be tried first if the result of the Thorn test is negative. The author feels that eventually it will be necessary to alernate between courses of ACTH and Cortisone where long-term therapy is planned. He feels very definitely that ACTH or Cortisone therapy should not be employed until all other forms of orthodox therapy have been tried without relief, and these drugs should not be used even then unless the patient is urgently in need of relief. While these drugs are being used intensive study of the patient as to possible etiologic factors should be continued. Another indication for the use of these agents is to clear the eczematous skin, at least temporarily, so that direct skin tests may be done instead of having to resort to passive transfer testing. The author did not notice any exacerbation of the eczema after treatment was discontinued, that is, the rash did not become worse than it had originally been. A further study was done in twenty patients with atopic dermatitis who were treated with cortisone ointment but the author was unable to show that the cortisone ointment helped any more than a control ointment in spite of reports in the literature stating that cortisone ointment is helpful. This paper clearly defines the indications for using ACTH or Cortisone in a child with eczema and is in agreement with the view of other authors.

Gay et al[31] report a study on eight patients, four of whom were suffering from contact dermatitis from medication, and four from Rhus toxicodendron dermatitis, or poison ivy. Only one of these patients was a child. Each patient was treated with one injection a day of corticotropic hormone for from two to six days. Each was greatly improved in from one to three days and completely recovered in from two to six days. The authors point out that the prophylactic desensitization by injections of ex-

tracts of specific plant antigens into patients suffering from poison ivy has been successful in a large number of sensitive patients but the treatment with antigens has been disappointing and of questionable value once a severe dermatitis has developed. The purpose of the present form of therapy is to enable the patient to remain ambulatory and to receive only one injection daily.

Downing[22] gives a review of the use of ACTH and Cortisone in dermatology. As this is a review of the literature it will not be further reviewed. The author, however, stresses the need for continued allergic control of these disorders during the time that the medication is being employed and emphasizes that cortisone in the treatment of atopic dermatitis should be confined to severe cases in which all conventional treatment has failed to arrest the progress of the disease.

Arbesman et al[3] studied intravenous ACTH and oral cortisone in the treatment of bronchial asthma. They gave intravenous ACTH therapy to twenty-eight patients with severe intractable asthma or status asthmaticus. Five of these had two courses of therapy. The patients ranged in age from six to seventy-one years, but it is not stated how many of the patients were children. Only the patients who failed to respond favorably to the usual anti-asthma medications were used in this study. Every patient showed an increase in both vital capacity and maximum breathing capacity after ACTH treatment. An increase in the maximum breathing capacity, however, was not always associated with a favorable clinical response. They also obtained good results with oral cortisone therapy.

McCombs[50] describes five patients with chronic, intractable asthma who were treated with repeated courses of ACTH or cortisone. Out of five patients, two were children, the others varied up to sixty-eight years of age. Symptomatic measures constituted the only other treatment. When the hormones were given in sufficient dosage soon after the occurrence of asthma, incapacitating attacks were avoided and an asymptomatic state was restored. The duration of remissions, however, was short, necessitating re-treatment on the average of once a month or less. The authors feel that in selected and supervised cases this form of therapy is practical from both medical and economic points of view but they point out that proved allergic management must not be neglected.

Schwartz[69] describes twenty-two patients with chronic intractable bronchial asthma who were treated with cortisone. Five of these were children. The author points out that these hormones do not work rapidly enough to relieve the asthmatic symptoms immediately or to save the patient's life in an acute allergic emergency, but feels that the symptoms are relieved within twenty-four to ninety-six hours after cortisone therapy is started. He concludes that the results justify the use of orally administered cortisone for symptomatic relief in intractable bronchial asthma after the usual therapeutic measures have failed but points out that cortisone therapy is not a substitute for allergic management.

Lockey et al[48] report nineteen patients who received treatment by the continuous intravenous infusion method of ACTH for the relief of status asthmaticus. The drug was found to be very dramatic in relieving the status asthmaticus and then it was found that the longer the time of administration the greater was the duration of the response. No toxic effects were encountered but the authors point out that these must be watched for as they sometimes occur.

In a symposium on ACTH and Cortisone, Glazer[33] reports eight children with intractable, perennial asthma, ranging in age from nineteen

months to fourteen years, all of whom cleared under ACTH or Cortisone therapy with remissions varying from twenty-four hours to three months. Occasional additional courses of the drug were required. Four additional children all under five years of age who had frequent severe asthmatic attacks at home were carried along on occasional ambulatory courses of ACTH.

Two long reviews of the use of ACTH and Cortisone in allergic states have appeared recently, one by Cooke[19] and the other by Brown[13]. As these are themselves exhaustive reviews on the subject, they will not be further discussed in this presentation.

## DRUG ALLERGY

During the past year, several papers have appeared in the field of drug allergy, most of them relating to penicillin sensitivity. Reyer[62] gives a classification of penicillin reactions with illustrative cases. His classification is as follows. *Group A*—epidermal contact reactions with localized dermatitis and with sensitizations restricted to the areas of application. *Group B*—dermal reactions regardless of the route of administration. Further classification includes: (1) Specific penicillin reactions limited to urticaria, a delayed reaction coming seven to twenty days after the administration of the drug. (2) Reactions to the vehicle, the base or the culture medium used to grow the penicillin. (3) Non-specific reactions to the common mold antigen. (4) Jarish-Herxheimer reactions to the disintegration toxins liberated from organisms killed by the penicillin. (5) Reactions caused by disturbance of the sympiotic balance of the skin organisms by the presence of penicillin. This seems to be a very practical classification of penicillin reactions as demonstrated by the author's illustrative cases.

Goltman[36] gives a general review of penicillin reactions, pointing out that the incidence varies from 3 to 5 per cent. He postulates seven possible mechanisms of pre-sensitization to medicinal penicillin. These are as follows:

1. transfer and sensitization *in utero,*
2. antigen-antibody reaction,
3. haptene formation,
4. common antigen effect,
5. inhalant antigen effect from the inhalation of penicillium mould,
6. ingestant pre-sensitization from the ingestion of penicillium mould and
7. penicilliosis.

It is often very difficult to understand why a patient who receives penicillin for the first time will show a sensitivity reaction and any one of these mechanisms can be the explanation in a given case.

Editorially in the *Journal of Allergy*[23] there is a review of the fatal allergic reactions to penicillin. This refers to five anaphylactic deaths from the injection of penicillin and refers to some other anaphylactic reactions to penicillin which were not fatal. It points out that such immediate reactions while far less common than the familiar delayed urticarial reactions, are more frequent than the medical literature indicates. The great majority of patients cited as having severe immediate reactions of this type had a past or family history of allergic disease of the hereditary or atopic type and many suffered from asthma. All had received numerous injections of either crystalline or procaine penicillin. In some instances, previous injections had

caused mild but definite immediate reactions, in others the severe or fatal reaction occurred suddenly after previous doses had been well tolerated. In none of the cases cited had development of sensitization to penicillin been accompanied by a delayed urticarial reaction similar to serum sickness. All the fatal reactions followed intramuscular injections but very severe and equally prompt reactions were reported after instillation of penicillin into the maxillary sinus, inhalation therapy and oral administration of the drug as tablets. Several of the patients who recovered from severe anaphylactic reactions subsequently showed immediate wheal reactions to scratch or intracutaneous tests with penicillin. In some instances Prausnitz-Kustner reactions were demonstrable. Intracutaneous tests on some of these patients were followed by severe constitutional reactions. These skin reactions were in striking contrast to the negative or questionable results noted in patients with the delayed urticarial type of reaction to penicillin.

The editorial continues that further studies will be needed to establish the actual value of skin tests and determine a proper technique of testing. Present indications are that scratch tests with solutions containing 10,000 to 50,000 units of crystalline penicillin per cc or intracutaneous tests with 0.01 to 0.02 ml of solutions containing 100 to 1,000 units per ml might serve the purpose. Suspensions of procaine penicillin in oil or water are apparently not useful for skin tests. There is no mention as to whether any of these reactions occurred in children, but the same general principles obviously apply.

Higgins and Rothchild[39] report a case of fatal anaphylactic shock from procaine penicillin. They point out that reactions following the administrations from penicillin are quite common, being reported in 5 to 10 per cent of all patients receiving the drug. The vast majority of the reactions are minor. They then summarize the anaphylactic reactions to penicillin which have been reported in the literature. These are seven in number, with two ending fatally. They find that their own case is the first case of an immediately fatal anaphylactic shock after the administration of penicillin in any form in which a physician was present to observe the reaction and in which an autopsy was performed. They discuss three kinds of penicillin reactions. (1) The urticarial serum-sickness like reaction, which usually appears three to ten days after administration of the drug has been discontinued, (2) The erythemato-vesicular eruption, which is much less severe, and (3) The third type which is extremely rare is immediate anaphylactic shock. They point out that it has been demonstrated experimentally that penicillin can cause anaphylactic sensitization in guinea pigs. The patient which the authors report is a fifty-seven-year-old man who had previously received procaine penicillin with no evidence of sensitivity. At the time of his death he received an intramuscular injection of 300,000 units of procaine penicillin G. One and a half minutes later he suddenly became cyanotic and died ten minutes after administration of the penicillin.

Smith and Walker,[72] in a monograph, review the papers which have appeared in the past ten years on both sensitization to penicillin and toxicities to the drug. This book brings under one cover a fairly complete discussion of sensitizations and toxicities to penicillin.

These papers on penicillin sensitivity very forcibly emphasize the dangers inherent in the use of one of the most useful drugs available to the medical profession and give adequate reason why the drug should be reserved for cases which really need it and why it should never be used in-

discriminately. Once a patient has shown a sensitivity reaction, it is very difficult to know whether it is safe to give the drug again.

Three general reviews on the subject of drug allergy have appeared during the past year. The first by Feinberg[25] is a general discussion on the subject of drug allergy and will not be summarized here. The second by Friedlaender and Friedlaender[28] reviews the cutaneous manifestations of drug hypersensitivity. The article concerns itself only with the cutaneous aspects of drug allergy, their immunology, morphology, incidence in relation to specific drugs and prevention and treatment of such reactions. Under immunological considerations, they point out that in those eruptions related to sensitization to protein drugs, immediate cutaneous whealing responses of circulating antibodies are frequently demonstrated. But, where nonprotein drugs are involved, whealing reactions of circulating antibodies are difficult and usually impossible to detect. As a rule skin tests in drug allergy are not of reliable diagnostic value. Even efforts to conjugate drugs with animal or human sera *in vitro* have been of questionable success in the diagnosis of specific drug allergy and the use of drug serum conjugates employing the sera of patients receiving a specific drug, although claimed by some workers to be of diagnostic value, has been found by others to be of little aid in the diagnosis of drug allergy. In discussing the morphology they point out that every type of basic dermatologic lesion may be reproduced and the same drug may elicit a variety of responses in the same as well as in different patients. Identical responses may be caused by a variety of chemically unrelated drugs, while varied morphologic patterns may be elicited by the same agent. Drug allergy must, therefore, always be considered in the differential diagnosis of every obscure skin eruption. Fixed drug eruption refers to a characteristic form of dermatitis which has the tendency to recur at the same site following the use of a drug to which the individual has become sensitized. The lesions may be single or multiple and are usually circumscribed patches several centimeters in diameter. The lesions may remain for a long time after their inception, usually in the form of pigmented patches and readministration of the specific drugs may cause an acute exacerbation at the same site. The authors list twenty-six drugs which are most commonly associated with the development of fixed drug eruptions. They also list the twenty-six drugs which have been known to give rise to exfoliative dermatitis. While many drugs produce eruptions identical in appearance, the lesions resulting from some of these present characteristic features which may suggest a probable etiologic agent. These features may be related to the character of the lesions, their persistence, their localization or their distribution. In table form the authors list the drugs grouped according to their pharmacologic actions, together with the types of eruptions which they have been known to produce. This list includes most of the drugs in common use today. The authors then described in detail the eruptions caused by specific drugs namely, the barbiturates, iodides, bromides, arsenicals, gold salts, sulphonamides, penicillin, streptomycin, dihydrostreptomycin, aureomycin, chloromycetin, terramycin, ACTH and Cortisone.

In a discussion on penicillin sensitivity they point out that the most commonly encountered reaction due to penicillin is the urticarial eruption, which may be mild in nature and disappear even while penicillin therapy is continued or it may be extremely severe and associated with the so-called serum-sickness type reaction. In their own experience they have found that it is not rare to encounter cases of chronic urticaria of several years' duration which were initiated by a serum-sickness type reaction fol-

lowing the use of penicillin. They do not believe that there is any proof for the supposition that there is a common antigen in penicillin and in certain of the pathogenic fungi responsible for superficial fungus disease and that the activation of the dermatophytic focus following penicillin is due to pre-existing sensitization to such pathogenic fungi. Furthermore they claim that there is no proved immunological relationship between penicillin and penicillium antigen. Many individuals who reacted quite violently to the early preparations of penicillin, have, in the author's experience tolerated present day commercial aqueous suspensions without untoward effects. The reliability of skin tests as an indicator of penicillin sensitivity is generally insufficient for routine clinical use. It has been claimed that patients who are sensitive to one type of penicillin, say penicillin G, can receive other types of penicillin without any difficulty. However, the duration of clinical sensitivity to penicillin is so variable that it is difficult to be certain that the patient who reacted to penicillin in the past and who subsequently tolerated the newer preparations, could not at the same time also have received the original kind of penicillin without reaction.

In a discussion of sensitivity to streptomycin they point out that cutaneous eruptions incident to streptomycin therapy are quite common, occurring in approximately 7 to 18 per cent of those receiving the drug. Eruptions are generally rare when the daily dose is one gram or less. Under treatment they point out that the principle in treatment of drug hypersensitivity reactions must be prompt recognition and withdrawal of the responsible agent. In each case, it must be decided how necessary the drug is to the patient and whether a suitable substitute can be given. Usually attempts to desensitize against the drug are unsuccessful and are fraught with danger. There is suggestive evidence that patients presenting certain dermatologic conditions are more susceptible to drug reactions and are prone to react unfavorably to many drugs, either with aggravation of the previous skin disease or with superimposed drug eruptions. They present a table of the common dermatologic conditions in which the patients tend to react to particular drugs and list the drugs to which they tend to react. The cutaneous manifestations of the drug reaction in many cases begin to subside shortly after withdrawal of the drug. In certain instances, however, the reaction may persist unabated for many weeks or months after administration of the drug has ceased. It is necessary therefore, to institute appropriate local and systemic therapy, and they feel that the antihistamine drugs have proved exceedingly helpful in controlling the urticarial and pruritic eruptions.

The third general review, by Carr[15] is a rather complete review on the subject of allergy to drugs and no attempt will be made to review it in detail. There were a total of 262 references. The article discusses a definition of allergic reactions as opposed to other types of drug reaction, the mechanism of allergy to drugs, certain manifestations of allergy that are provoked exclusively or most commonly by drugs, certain drugs that deserve special attention as allergens and some aspects of diagnosis prevention and treatment of allergic drug reactions. The article includes a long list of the drugs which have been reported as causing exfoliative dermatitis, a table of the drugs which probably cause bone marrow depression in man according to whether the result is agranulocytosis, thrombocytopenic purpura or aplastic anemia, and a list of drugs which are reasonably well established as the cause of certain allergic reactions in man. In this latter list, the drugs are listed according to those which cause urticaria, angio-

neurotic edema, asthma, dermatitis which is not contact in nature, contact dermatitis and fever without other allergic manifestations. These tables include references to the literature where the individual cases are reported and are very valuble as an easy means of reference.

### VIRAL AND RICKETTSIAL VACCINES

Ratner et al[57,58,59] in a series of three papers discuss experiments done with viral and rickettsial vaccines, chiefly in relation to the incidence of egg allergy. In the first paper they report a study of the incidence and interpretation of egg sensitivity in both allergic and nonallergic children. In a study of 322 so-called nonallergic children, egg sensitivity as judged by the presence of clinical sensitivity and a positive skin test was found in only one patient, or 0.3 per cent, which agreed with their previous estimate that only 0.5 per cent of the general population were sensitive to egg sufficiently to warrant special precautions in the administration of chick embryo-propagated viral and rickettsial vaccines. They also studied 500 known allergic children and found that 20.4 per cent of these were skin sensitive to egg white but that only 5.6 per cent of the entire group were clinically sensitive to egg white as well. The remainder of 20.4 per cent had a residual skin sensitivity without clinical significance. They found that the incidence of egg white sensitivity waned with age and was much more common in young, allergic infants. They conclude that the diagnosis of egg sensitivity cannot be made on the basis of skin tests alone, for positive skin reactions to egg outnumber the clinical significance. A positive skin reaction to egg may connote (a) a residual skin reaction in a person who has long overcome his clinical intolerance, (b) a limited tolerance for egg or (c) a marked clinical intolerance for egg. A negative reaction may, on occasion, be encountered in a person with a marked clinical sensitivity hence the skin reaction must be considered in relation to the complete clinical picture.

In the second paper is reported a study of the responses to egg embryo cultured vaccines, both influenzal and mumps in type, injected for immunologic or diagnostic purposes into allergic subjects. First of all the authors review the literature on reactions to viral and rickettsial vaccines and point out that all types of reactions have been found, namely, fatal anaphylaxis, severe anaphylaxis with recovery, moderate systemic allergic reactions, serum sickness-like reactions, consisting of systemic reaction of the accelerated type, a local reaction of the accelerated type, typical serum sickness-like reaction, a local serum sickness-like reaction, and also immediate dermal reactions and local delayed dermal reactions. They then report a study of the dermal reactions to influenzal vaccine using three types of the vaccine, (1) a red blood cell eluate vaccine, (2) Sharples centrifuge-type vaccine, and (3) alcohol precipitated vaccine. They studied these both by intradermal testing for the study of hypersensitivity reactions and also by test and prophylactic injections of the vaccine. These were done on children who were known to be exquisitely sensitive to egg protein, in those who were known to be moderately sensitive and in those who were known to be clinically immune to egg, even though they did have residual dermal sensitivity. Similar studies were done with mumps vaccine. Influenza A and B virus vaccines were also given prophylactically to 248 allergic children who were shown to be not sensitive to egg and in not a single instance was any allergic reaction to vaccine noted. The diagnostic test for susceptibility or immunity to mumps was repeatedly performed on

ninety-three allergic children not sensitive to egg. In no instance was there any untoward reaction with the mumps vaccine so employed. The study showed that there was a direct relation between allergenicity and the chick embryo protein content of the vaccines. The red blood cell eluate vaccines contained the greatest amount of egg protein and elicited the greatest reactions while the Sharples centrifuge or alcohol precipitated vaccine had fewer reactions and the latter was perhaps the least allergenic.

They conclude that the criteria for determining the allergic hazard prior to therapeutic use of the vaccine can be evaluated as follows: (a) An intradermal injection of 0.02 cc of the vaccine is of prime value in determining the degree of sensitivity. (b) If a systemic reaction ensues, it is evidence of a high degree of sensitivity. The vaccine should then be withheld or given in small diluted and fractionated doses, preferably intradermally in conjunction with several minims of epinephrine. (c) If only a large local reaction ensues with the test dose, the vaccine can be diluted and administered with 2 minims of adrenalin. (d) A history of sensitivity to egg, while valuable, is not as reliable a criteria as the intradermal test with the vaccines itself.

With purified influenza vaccine, poor in egg protein, it was determined that 0.1 to 0.15 cc may safely be given intradermally or subcutaneously with the added precaution of 2 minims of epinephrine to moderately or even highly sensitive egg subjects. With mumps virus vaccine, which is also reduced in egg protein content, the test dose of 0.05 cc intradermally was well tolerated by egg sensitive subjects. No reactions were noted in several hundred non-egg sensitive allergic children, repeatedly given injections of influenza and mumps vaccine. Reaction in certain non-egg sensitive children was shown to be due to the formalin incorporated in the vaccines. They believe that the allergic hazards and unnecessary deaths which have resulted in the use of viral and rickettsial vaccines can be eliminated (1) by the reduction of egg protein-content of such vaccines, (2) if due regard is given to the criteria herein set forth for determining sensitivitv prior to the administration of such vaccines, and (3) if due caution is exercised in the use of these vaccines in egg-sensitive subjects.

In the third paper they report a study of the problem of the possible acquisition of hypersensitivity to egg protein from repeated injections of vaccine derived from viruses or rickettsiae propagated on chick embryo. They studied this on allergic and normal children to determine whether repeated injections would provide sufficient allergic stimulus to result in the acquisition or enhancement of egg allergy. Studies were done on 319 nonallergic children. These were injected with chick egg-propagated influenzal viral vaccine or mumps viral vaccine or both. The children were given repeated injections of the vaccine and were tested intradermally for sensitivity to egg proteins. Injections were given at varying intervals over a period ranging from twelve to twenty-seven months. The total number of injections per subject ranged from eleven to thirty-five. In five subjects or 1.6 per cent, there was a development of dermal sensitivity to egg white, but in no case was clinical egg sensitivity induced. Twenty egg-sensitive children were studied and in none of these was there noticed any enhancement of clinical sensitivity after repeated inoculations of crude and refined influenzal virus vaccines. However, one child who was known to be intolerant to egg developed a generalized urticarial rash within one hour after the injection.

Studies were done on 120 allergic children who were sensitive to substances other than egg. These were followed over a period of one year and

no egg sensitivity was found to be acquired after repeated therapeutic injections. This suggests that children, allergic to substances other than egg, are no more prone to develop hypersensitivity to egg from this vaccination than are non-allergic persons. The authors conclude that within the limits of their data, the hazard of sensitization from repeated re-injection of viral and rickettsial vaccines seems negligible.

These three papers contribute towards our knowledge of both egg allergy in children and also towards our knowledge in the clinical use of influenzal and mumps vaccines. The criteria laid down for determining the allergic hazard prior to therapeutic use of the vaccines can be applied to all vaccines which are prepared by culture on chick embryo. These include those of yellow fever, typhus, rocky mountain spotted fever, tick typhus, equine encephalomyelitis, influenzal A and B strains of virus and mumps vaccines. If these criteria are followed before any of these vaccines are injected in the human subject serious reactions should be negligible. The reassurance that repeated injections of these vaccines are not apt to lead to sensitization of the subject who is not allergic to egg, nor to increase the sensitivity of the subject who is already sensitive to egg, is very reassuring both to the physician who has to give these injections and to the patient who has to receive them.

## DIET MODIFICATIONS

Glaser and Johnstone[34] report on soy bean milk as a substitute for mammalian milk in early infancy with special reference to the prevention of allergy to cow's milk. They postulate that if the protein which constitutes the chief source of food and is most commonly the cause of a multitude of clinical allergic phenomena, that is cow's milk, were withheld completely from the infant's diet during the period of physiologic and immunologic immaturity the symptoms of milk allergy might be avoided, minimized or even prevented. They chose their cases from families in which one or both of the parents were allergic or in which there was at least one allergic child and the arrival of another infant was expected. The expectant mother was placed on a diet designed to prevent excessive ingestion of antigens which might sensitize the infant *in utero*. If she chose to nurse the baby subsequently, this diet was continued. At birth the infant was placed on a soy bean milk, either as a sole source of food or as a complimentary feeding. The milk substitute used was Mulsoy, the starting formula using one-third Mulsoy and two-thirds water which was gradually increased as tolerated to a formula of equal parts of Mulsoy and water. The hospital record of every child was reviewed for notes concerning intestinal disorders or possible evidence of intolerance to soy bean milk. Each baby was examined and re-evaluated approximately monthly during the first year. The record of each child was carefully reviewed for signs of intolerance to soy bean milk or any other allergic phenomena during the period that the soy bean milk was given and following the final introduction of cow's milk to the diet. The authors did not find any evidence of any difference in the growth and development between the group that had soy bean milk and infants of comparable age and social and economic background. Of sixty-seven infants, nine or 13.5 per cent, were thought to be intolerant to soy bean milk during the neonatal period. Symptoms necessitating the discontinuance of soy bean milk in these nine infants were diarrhea, vomiting, colic and atopic dermatitis. Three infants developed atopic dermatitis while on the soy bean milk, but only one case

was severe and suspected of representing a true intolerance to Mulsoy. The authors conclude that the preparation of soy bean milk may be used successfully in over 85 per cent of cases to feed infants from birth and that these infants may later be changed over to cow's milk formulae without difficulty, except in those cases where there is probably a persistent congenital sensitivity to cow's milk.

This paper demonstrates for the first time that a preparation of soy bean milk may be used successfully to feed infants from birth and that this may be applied to the feeding of infants from allergic families so that there may be a greatly lowered incidence to sensitivity to cow's milk in later life. An extension of the same principle to other foods shows how sensitivity to other important foods such as egg and wheat may also be minimized in allergic infants.

These same authors[35] report on the use of meat as a source of protein in milk substitutes in allergic gastrointestinal disorders of early infancy. They studied a number of infants in the newborn period and in very early infancy without atopic dermatitis but with gastrointestinal disturbances, apparently due to allergy to cow's milk, which did not respond to substitution of soy bean milk. These infants were successfully treated with meat milks. The authors give a recipe for the preparation of this meat milk. They include cases of three infants who did very poorly on cow's milk, having colic and diarrhea and other gastrointestinal disturbances and who also did poorly on soy bean milk, but they did well on the meat milk mixture. They conclude that the use of meat as a source of protein in allergic gastrointestinal diseases during the newborn period and early infancy, when these conditions are due to allergy to cow's milk, or intolerance to soy bean milk, is a practical and useful procedure. When relief is obtained by the use of meat milks, it is striking and rapid, occurring within the first twenty-four hours of use.

Tomarelli et al[74] discuss the nutritional quality of milk which has been thermally modified to reduce its allergenic reaction. They point out that the prolonged heat treatment of milk to reduce cow's milk protein antigen has proved of value in the feedings of infants or children allergic to cow's milk. They say that preliminary experiments have demonstrated that the drastic thermal effect required for the denaturation of the milk protein results in the impairment of nutritional quality, as evidenced by the depression of growth rate of young rats fed heat-modified milk. They found that young rats fed heat-treated milk fortified with minerals and all the usual vitamins with the exception of vitamin $B_{12}$, grow at the sub-optimal rate but that the addition of liver powder or of a vitamin mixture containing vitamin $B_{12}$ to the heat-treated milk, results in a growth rate equal to that of rats fed on unheated milks.

This paper purports to show that evaporated milk is not a suitable food for the growing infant. However, these findings on rats cannot necessarily be carried over to the human infant because it has been noticed repeatedly that human infants grow normally when they are fed on evaported milk mixtures. Moreover human infants do not rely solely for the source of vitamin B on the milk as did the rats in this experiment. Thus, this paper does not in any way change our present attitude towards the feeding of allergic infants with evaporated milk.

## GASTROINTESTINAL ALLERGY

Two papers have appeared on gastrointestinal allergy in children. Fries[29] reports some roentgen studies of allergic children with disturbances of their pylorus resulting from food sensitivity. He points out that it is becoming increasingly apparent that the pylorus plays a major role in the allergic symptomatology of the stomach and that any survey of the many factors underlying pyloric obstruction must include hypersensitiveness. He studied thirty allergic children ranging in age from four to fourteen years, all of whom had repeatedly exhibited marked gastrointestinal disturbances, vomiting, abdominal cramping, nausea, and epigastric distress within a few minutes after ingestion of small amounts of the offending foods. Many of these patients showed positive intracutaneous reactions with the offending food. In a control study roentgenographic examinations were made with the patients swallowing plain barium sulphate and water. Approximately a week later, a similar study was made employing barium sulphate and water to which the offending allergen was added without the knowledge of the patient. The authors found that allergic reactions occurring in the stomach following intestinal feeding of these antigenic substances, were often most pronounced in the pyloric area. There was gastric retention in these patients attributed mainly to blockage of the pylorus. Re-exposure to the same allergens produced the same results.

This study throws further light on the gastrointestinal symptoms which follow the ingestion of food to which the patient is allergic and points out that pylorospasm can be caused by sensitivity to a food.

Rosenblum and Rosenblum[65] report a series of sixty infants having gastrointestinal disturbances which appear to be on an allergic basis and attempt to correlate the clinical evidence of allergy with a demonstration of stool eosinophilia. The sixty infants suffered from diarrhea, vomiting and colic, either alone or with two or three of these in combination. A decided stool eosinophilia was demonstrated in all. They also studied seventy-six infants whose stool smears were negative for eosinophils and these included cases of bacillary dysentery, cystic fibrosis of the pancreas, amoebic dysentery, diarrheas of undetermined cause and normal infants having normal stools. There was nothing in the clinical course of these seventy-six cases to indicate any evidence of active allergy during the period of observation. In the milk allergies they found that mild cases often responded to evaporated cow's milk. It was found that after six to nine months of age, most of these infants could tolerate cow's milk. In many cases of proved sensitivity to milk, skin tests were negative.

This paper discusses one aspect of the very important problem which confronts every practising pediatrician, namely, vomiting, diarrhea and colic in the small infant. The paper points to one of the causes of these conditions, but it is important to remember that allergy is not the only cause of these conditions. Many further careful studies are necessary in order to further evaluate this problem and a more widespread use of examination of the stools for eosinophils is necessary as this appears to be a valuable tool in evaluating the problem. However, this is an extremely difficult method, and for this reason may never be popular.

## IMMUNOLOGY

Wiener[77] makes an important contribution in a paper in which he draws on his prolonged study of the Rh factor to come to certain conclusions about antibodies, particularly as applied to the field of allergy. On the

basis of his studies he makes several observations which are of interest to allergists. While univalent antibodies are apparently responsible for one's immunity to pathogenic micro-organisms, bivalent antibodies appear to be the basis for the various allergic phenomena. The antibodies which first appear are often of the bivalent variety, but these generally disappear after a short time and are replaced by univalent antibodies. Actually there is evidence that in most cases the production of bivalent antibodies continues, but the presence of these antibodies is not readily demonstrable as they are prevented from acting by the more potent univalent antibodies present in the same serum. Exceptional individuals will produce excessive amounts of bivalent antibodies and perhaps it is such individuals who, under favorable conditions of exposure, are more likely to develop allergic disease. The natural course of the production of antibodies explains the value of the hyposensitization injections which are given for asthma and hay fever. When the injections are repeated, not only does the titre tend to rise but the quality of the antibodies changes as univalent antibodies replace bivalent antibodies which were originally present. Thus the body is caused to form a high titre of specific blocking or univalent antibodies so that when the individual is exposed to the antigen later on, the blocking antibodies combine with the antigen and thus prevent the reagins, that is the bivalent antibodies, from doing so. Inasmuch as allergic manifestations generally accompany the *in vivo* combination of antigen with bivalent antibody and not with univalent antibodies, allergic individuals treated in this way are usually benefited. Bivalent Rh antibodies usually disappear within a relatively short time but the univalent antibodies remain and decline in titre only gradually over the years. Similarly, in the case of allergic individuals if all contact with the offending allergen is avoided the reagins tend to disappear while the blocking antibodies persist. The anamnestic reaction is defined as the accelerated and exaggerated immune reaction which follows the re-injection of the specific antigen after a long interval. This reaction can easily be demonstrated by the injection of Rh positive blood into Rh negative persons and the observations from this reaction fit with the observation that allergic individuals are generally most severely affected by antigens with which contact occurs at wide intervals, namely pollens and seasonal foods. In the interval between the exposures the reagins tend to disappear, but on re-exposure they presumably rapidly re-appear in high titre (anamnestic reaction) and cause allergic manifestations. If continuous contact with the allergen is maintained as in the perennial treatment of hay fever or daily ingestion of a food, the reagins then decline in titre, while potent blocking antibodies are formed so that immunity replaces hypersensitiveness.

Kuhns and Pappenheimer[44,45] report in two papers on studies of the antitoxin produced in normal and allergic individuals hyperimmunized with diphtheria toxoid. This study was prompted by the authors seeing a six-year-old boy with a personal and familial history of allergy who was brought to the hospital in a severe asthmatic attack precipitated within a few minutes following a routine booster dose of diphtheria toxoid. Subsequently, minute amounts of purified diphtheria toxoid given intracutaneously produced marked wheal and erythema reactions with pseudopodia. Even minute amounts of toxoid caused pronounced skin reactions. This specific sensitivity to toxoid could be passively transferred to normal skin sites. The serum from the patient showed an antitoxin titre of 50 units per cc by rabbit skin test but contained no precipitating antitoxin whatever. This behavior was quite unusual since in previous studies the

sera of a large series of normal subjects, hyperimmunized with purified toxoid, had all shown good precipitin reactions. They then tested 131 medical students with purified diphtheria toxin using purified toxoid as control. There were forty immediate reactions to the toxoid, thirty-five of these occurring in patients who claimed personal or familial allergic histories. Five occurred in students claiming no personal or familial allergic history. They then made a study of the presence of non-precipitating antitoxin in the sera and in twelve of thirty the sera from hyperimmunized subjects showed the presence of considerable amounts of non-precipitating antitoxin. Moreover, sera from three patients failed to precipitate at all with toxin, despite the presence of 20 or more units of antitoxin per cc by *in vivo* titration. However, the proportion of individuals showing considerable non-precipitating antitoxin was no greater among the allergic group than among those who disclaimed all knowledge of familial or personal allergy. In fact, the three individuals who produced no precipitating antibody whatever, despite high titres of non-precipitating antitoxin, denied any history of personal or familial allergy. There was a marked parallelism between the severity of the skin reactions observed and the presence of demonstrable amounts of non-precipitating antitoxin following the booster dose of toxoid. Thus, the authors have demonstrated in this study that antibodies to diphtheria toxoid may consist of both the classical antitoxin which is precipitating antibody and also antibodies of the same nature as occur in the allergic individual which are non-precipitating antibody. This points out that diphtheria toxin and toxoid may be used as a model for the study of the hay fever-type of allergy. Since these materials can be obtained in pure form and can be measured accurately in the serum they can be used in this study much more satisfactorily than can pollens and other antigens.

In their second paper they extend these studies to describe the contrasting immunologic properties of precipitating and non-precipitating human diphtheria antitoxin, both *in vivo* and *in vitro*. Sera which contain only non-precipitating antitoxin, exhibit most of the properties of atopic reagin-containing serum. This type of antitoxin is capable of sensitizing normal human skin to toxin or toxoid and remains for many weeks in the injected area. It is capable of sensitizing guinea pigs to fatal anaphylactic shock, it does not fix complement unless very large amounts of serum are used. Heating at 56 degrees centigrade for four hours destroys the skin-sensitizing properties and results in almost quantitative conversion to modified antitoxin, which is capable of blocking the wheal and erythema reaction caused by the injection of toxoid in a sensitized skin. Precipitating antitoxin is incapable of sensitizing normal skin to toxin or toxoid and disappears rapidly from the injected sites. It fixes complement in high titres and sensitizes guinea pigs to fatal anaphylactic shock. The two antitoxic sera in the study represent extreme cases. Many patients immunized with toxoid develop both precipitating and nonprecipitating antitoxin simultaneously. These studies give us a better insight into the nature of the allergic antibody and its relation to the immune antibody.

Halpern et al[37] studied the effect of cortisone on the level of serum antibodies in rats sensitized against ovalbumin during the period which follows the challenging injection of a neutralizing dose of antigen.

It was found that in the first forty-eight hours following the injection of antigen the level of the antibodies in the sera of the treated rabbits was significantly higher than that of the control animals. After the third day, on the contrary, the production of the antibodies of the treated animals

was found to be much lower than that of the controls. The authors believe that the remarkable increase in the serum antibody level which is observed in the first forty-eight hours is due to the release of antibodies under the stimulation of hormones upon the lymphatic tissue. They observed the considerable lysis of lymphocytes in these animals, and parallel studies of the serum antibody levels and of the number of lymphocytes in the blood and tissues showed that as the antibody level increased, there was a corresponding drop in the number of lymphocytes in the blood and lymph nodes. They explain the decreased production of antibodies after the third day in cortisone-treated animals on the basis that there is an inhibition by the hormone of antibody production by the cells of the reticuloendothelial system which produce them normally.

Since so many patients at the present time are receiving ACTH and cortisone to control their symptoms at the same time as they are being actively hyposensitized against various allergens, the answer as to what effect these drugs have on antibody production is very important. This paper contributes some information on the effect on the serum antibody levels during the early part of cortisone therapy but it does not answer the question as to long-term results of cortisone therapy on the final antibody level of the patient who is being hyposensitized. Experience with these drugs, during the time that hyposensitization is being carried out, would appear to indicate that a patient is capable of producing immune antibodies even while these drugs are being used.

Laurent and Parish[46] discuss serum reactions and serum sensitivity tests. These authors condemn the use of the usual sensitivity tests such as intradermal, ophthalmic and scratch tests becase of false positive reactions and false negative reactions which they believe occur so frequently as to make these tests practically useless. They prefer rather to use trial doses of a serum subcutaneously in order to test for general reaction as opposed to local reaction. The following are their procedures:

First of all the history must reveal whether the patient has had serum before and whether the patient has suffered from asthma, infantile eczema or other allergy. If the answers to these are negative, the required dose of serum may be given intramuscularly for prophylaxis or treatment. The patient must be kept under observation for one-half hour. If no untoward effects are noted within this period it can be assumed that nothing dangerous will subsequently develop. However, the patient should be warned about the possible subsequent development of serum sickness. If there is a history of a previous injection of serum, a small trial dose of 0.2 of a cc of undiluted serum is injected subcutaneously or even 0.1 of a cc may be used. The patient is kept under observation for half an hour and if no general symptoms develop, a full dose of serum may then be given intramuscularly as required for prophylaxis or treatment. Once again observation for half an hour is necessary. If there is a history of allergic asthma, infantile eczema or other allergy, the patient should ideally not receive serum at all as the risk of anaphylactic shock is considerable. If serum is necessary the patient should first receive a subcutaneous trial dose of 0.2 of a cc of one in ten dilution of the serum. The patient is kept under close observation for one-half hour. If there is no general reaction he is given 0.2 of a cc of undiluted serum subcutaneously and once again observed for one-half hour. If there is no general reaction the patient is not likely to develop subsequent severe anaphylaxis and is then given intramuscularly the full dose of serum required for prophylaxis or treatment. Once again he is kept under close observation for one half hour. In those

severe cases where intravenous injection of serum is indicated, before the intravenous route is used, the preliminary procedures described above for an intramuscular injection should be always carried out. It is neither wise nor safe to give an intravenous injection of serum, regardless of the skin sensitivity test, as a first step in treatment and without a preliminary intramuscular injection that has been tolerated by the patient. Ideally, two hours should elapse between the intramuscular injection and the intravenous injection and even in cases of great urgency never less than one-half an hour.

The intracutaneous and ophthalmic tests are safe and reliable criteria for determining a high degree of sensitivity and far less dangerous than the procedure suggested in this article.

## PSYCHIATRIC ASPECTS OF ALLERGIC DISEASE

Abramson,[1] in a paper on the psychodynamic pharmacology of the treatment of asthma, stresses the fact that in the treatment of the asthmatic patient the physician should not ignore the personaliy of the patient in planning suitable therapeutic procedures. He should use pharmacologically active drugs in connection with the total personality of the patient manifested during the acute asthmatic attack, whether anxiety, phobia, depression, dependence, hosility, grief, euphoria or other pattern dominates the attack. He discusses each of these types of patients separately and gives examples. In the anxious asthmatic patient, for example, it is important to search for symptoms connected with anxiety. In such a patient, epinephrine by injection or inhalation or ephedrine and related substances should be used in small doses because these drugs are likely to produce more anxiety if given in larger doses. The depressed patient, on the other hand, often prefers epinephrine by injection rather than by inhalation, because of the stimulating effect of the injected epinephrine. The depression should be treated cautiously by the administration of amphetamine sulphate after breakfast and after lunch. However, epinephrine is not contraindicated. In the grieving patient it is important to recognize the state and to make certain that the physiologic needs of the patient are taken care of with suitable reassurance and minimal use of sedatives and sympathomimetic amines. Breathing exercises are often helpful here. In the hostile asthmatic patient the sympathomimetic amines either by injection or aerosol should be used with caution. In this type, sedation is often effective. In the dependent asthmatic patient, particularly the child who makes neurotic utilization of the asthma in order to obtain attention from the parents, it is sometimes necessary to remove the child for a considerable length of time from the parents. In the euphoroid asthmatic patient it is particularly necessary to take a careful history because such patients may even deny that they have asthma. The phobic asthmatic patient has fundamentally emotional problems and these should be handled as such.

This paper is a careful and systematic study of many of the psychologic aspects of asthma and the author very ably shows how categorizing the patients according to this system also indicates the type of therapy that should be used in the treatment of the acute asthmatic attack.

Two books have appeared in his field. The first, by Abramson,[2] is a complete review of the subject of allergic asthma. It consists of chapters written by thirty-four different contributors, all authorities in their fields. Most of the book deals with asthma in general and is referable both to children and adults but there are chapters referring specifically to pedi-

atric allergy. A chapter on asthma in children by Ratner is a complete review of the subject of asthma in children.

The second book, by Baruch and Miller,[8] deals with the psychosomatic aspects of allergy. It consists chiefly of the psychologic and psychiatric study of a boy suffering from severe asthma and of similar studies in his parents. Emotional causes of the asthma were found based on the parents' lack of adjustment to each other, the child's maternal grandmother and the reactions of the child to his parents. With prolonged psychosomatic therapy the boy became well adjusted and his asthma disappeared.

### MISCELLANEOUS

Ratner and Silberman[60] discuss the hereditary concept of allergy. They made a study of 250 allergic children and their families and the children ranged in age from infancy to sixteen years. Detailed histories of the family history of allergy were taken repeatedly by questioning both father and mother. The manifestations which were regarded as allergic were asthma, hay fever, eczema and recurrent urticaria. They point out that discrepancies noted in published observations on the distribution of allergy and its relation to heredity are largely due to the different methods of collection of data, the criteria employed in defining the allergic state and the extent to which the inquiry was made into the individual and family incidence of allergy. An extensive list of the authors who have made similar studies on allergic family histories is given and both this series and those reported in the literature showed a positive family history in approximately 50 per cent of allergic patients. Studies of the family tree of these 250 patients revealed that approximatly 10 per cent suffered from major allergies, that is, asthma, hay fever, eczema and recurrent urticaria. This same percentage was found on questioning a random population of 3,000 individuals and several reports from the literature indicate that about 10 per cent of the random population have major allergies. In other words, the frequency with which these syndromes occur in so-called allergic families or general population is the same. On the other hand, about 50 per cent of the random population have minor allergies. Further studies revealed that the families which had only one to three allergic members including the patient comprised the large majority of the entire group of the 250 family trees. Relatively few of the families had a large number of allergic individuals in them. In other words the concept that it is characteristic of allergy to appear in a large number of members of so-called allergic families is not supported by the data. While allergy may appear in fairly large numbers in a certain few families, this is not the general trend. The authors feel that the view that it is the trend is based chiefly on a few striking family pedigrees which have been recorded in the literature. The authors could find no evidence from their data that the mendelian laws of inheritance of allergy were being followed and do not believe that any genetic hypothesis can be made to fit the existing data.

Matheson et al[49] discussed the reactivity of the skin of the newborn infant. In an attempt to clarify the situation they performed four sets of experiments. (1) Skin tests were done on newborn infants with serial dilutions of histamine and comparison of the results was made with similar testing of older children. It was found that the skin of a full term newborn infant reacted to various dilutions of histamine phosphate with erythema but no wheal formation as contrasted to the skin of older children where whealing was frequent. (2) They studied the fixation of reagin

by the skin of newborn infants full term and prematurely born. By passive transfer tests it was shown that the skin of the full term newborn infant was capable of fixing reagin locally with a tendency to smaller wheals in premature infants of varying ages and weight. (3) They demonstrated cutaneous reactions in passively-sensitized sites of newborn infants following the ingestion of the specific antigen. It was found that the skin sites passively sensitized to egg showed erythema and whealing following the feeding of whole raw egg to both newborn infants and older children. This suggests that products of protein digestion or proteins of sufficient complexity to be antigenic are absorbed from the gastrointestinal tract of both newborn infants and older children. (4) They demonstrated cutaneous reactions in passively-sensitized sites of newborn infants following the subcutaneous injection of specific antigen. The skin of the infants was sensitized by intradermal injection of specific egg-sensitive serum and subsequently dilute egg white was injected subcutaneously at other sites. The sites prepared with the undiluted serum revealed reaction to the peripheral subcutaneous injection of egg white with erythema and wheal formation; thus showing essentially the same findings as had been demonstrated in the feeding experiment.

The above experiments support the view that the skin of the newborn infant is capable of demonstrating an antigen-antibody reaction and that such reaction may be in the nature of erythema or whealing.

During the past two years there has been a great deal of discussion on the relationship between inoculations and poliomyelitis. This has caused a great deal of confusion both in the minds of the profession and of the public as to the advisability of giving inoculations during the poliomyelitis season. This question is summarized editorially in the *Journal of Allergy*[24] which prints part of the Public Health reports of May, 1952, Vol. 67, and discusses a meeting held by the Public Health Service, which was attended by forty-two poliomyelitis investigators, epidemiologists, pediatricians, allergists and health officers; the conference voted unanimously in favor of the conclusions contained in the following statement which has been accepted by the Public Health Service.

"There is no definite evidence that an increase in the number of cases of poliomyelitis has occurred as a result of injections of vaccines, drugs and other medicinal agents. There is evidence that injections for the prevention of diphtheria, whooping cough and possibly tetanus, when given during an epidemic of poliomyelitis may, on rare occasions, localize the paralysis in the inoculated arm or leg. There is no satisfactory evidence that other types of injections have any effect on the localization, frequency, or severity of poliomyelitic paralysis. Certainly no parent should object and no physician should hesitate to administer a needed antibiotic drug or other injection for treatment of disease at any time."

Friedewald[27] discusses the question of whether skin testing in allergic patients is worthwhile. To determine the value of skin tests to foods and inhalants he reviews 1,900 allergic private patients on whom an average of seventy tests each were performed. He lists the positive inhalant reactions and the positive food reactions and the percentage of positive skin tests of clinical importance to various allergens in the different disease groups. From his study he concludes that food testing is time consuming, expensive and not important in most instances and lists the foods that should be tested for in hives, hay fever, asthma, and in both childhood and adult eczema. He concludes that skin testing is a safe procedure if proper

precautions are observed and that skin testing is worth the effort since it very often serves as a short cut to the finding of the offending agent.

This conclusion is one which will be agreed with by practicing allergists. Although many attempts are made to discredit skin testing, observations on the little value of skin tests usually come from people who have had very little experience with them in order to evaluate their worth.

Levin[47] discusses the optimum dose of pollen in the treatment of pollenosis in children. It is his belief that the maximum tolerated dose is the optimum dose for the pollen-sensitive patient, and for this reason he treats his pollen-sensitive children with large doses, generally starting them off with .05 cc of 1:10,000 solution, weight per volume, and working them up to 1 cc of 1:33 dilution, that is, a 3 per cent solution. This is the schedule he uses for cases of average sensitivity but initial and top doses will be lowered for more sensitive patients. Usually, the higher the degree of skin sensitivity the lower the top dose necessary to produce good results. He does not feel that quantitative skin tests by the method of serial dilution intradermally help enough in either children or adults to make this method worth doing as routine procedure. He judges the skin sensitivity of the patient by using first the scratch test and then the intradermal test with 1:100 dilution if the scratch test is negative, and then an intradermal test with 1:33 dilution if the 1:100 dilution has been negative. Rarely does he find a pollen-sensitive child who does not react to the 3 per cent extract intradermally. The above dosage schedule refers only to pre-seasonal and perennial desensitization. For co-seasonal treatment for a patient not previously treated he does use small intradermal injections at one to three-day intervals. He finds that children tolerate high pollen dosage at least as well, if not better, than adults. The best guide to pollen dosage is the local reaction, provided important factors other than dosage are considered; these are depth of injection and irritation due to extracting fluid used. In his experience general reactions occur with relative infrequency despite the high dosage used in hundreds of pollen-sensitive children. The results of this high dose therapy in pollen-sensitive children were excellent. Eighty per cent of the patients received excellent results the first year of such pre-seasonal treatment, 50 per cent could discontinue treatment in three to five years of continuous pre-seasonal and perennial therapy when treatment was carried out according to the outlined method.

While this paper presents evidence strongly in favor of the high dosage method of treatment of pollenosis, it must be remembered that a great many allergists who use much smaller doses report equally successful results.

Hansel,[38] in a paper on sinusitis which refers to both adults and children, points out that the immunologic methods in the treatment of sinusitis concern the management of infection, allergy, and allergy with infection. The management of infection concerns the use of vaccines, either mixed respiratory in type, or A and B virus vaccines or staphylococcus toxoid, and also the use of antibiotics. The allergic management includes immunization to pollens, dust, animal danders, atmospheric molds, foods and also hormonal therapy such as ACTH, cortisone, thyroid, estrogens, androgens, et cetera. He points out the solution of the problem of the management of sinusitis is today comparatively simple. Accurate diagnosis must be made depending on the clinical history, local examination, cytology of secretions, bacteriology, x-ray examination and pathologic examination of the tissues. For allergic immunization with the bacterial vaccines, he recommends a low dosage method, using dilutions of the order of 1:100,000 and

1:1,000,000 rather than a high dosage method, which is worked up to a concentration until the point of maximum tolerance is reached. He feels that better results are obtained with the former method.

Clein[16] gives his views on the question of tonsillectomy and adenoidectomy in allergic children. He points out that if absolute indications exist, surgical removal of the tonsils and adenoids in children is followed by gratifying results and that relief of symptoms occurs in a short period of time. The absolute indications are: (1) repeated tonsillitis usually with fever, (2) cervical adenitis following sore throats, (3) otitis media, (4) systemic infection and/or poor nutrition resulting from repeated attacks of tonsillitis, (5) nasal obstruction and mouth breathing from obstructing adenoids, (6) abscess of the pharynx, tumors or injury of the tonsils and fetor oris from debris in the crypts of these structures. On the other hand, in a fairly large percentage of children who undergo tonsillectomy, the outcome is not favorable. The symptoms often become more pronounced than they were before operation and in many of these unsuccessful cases the underlying cause may be other than that of infection, although the major symptoms are the same. Previously unrecognized or untreated allergies are responsible for these failures more than any other reason. In those children where the symptomatology is due to allergy rather than due to infection as listed under the absolute indications, it is desirable to treat the allergic symptoms first and when the allergy is under control to consider removal of the tonsils and adenoids. These operations should be performed only if there are the same indications as in a nonallergic child. Unless this plan is followed the effects of operation may be harmful instead of beneficial. Asthma has been precipitated by the removal of tonsils and adenoids in children with seasonal hay fever, especially during the pollen season. After the tonsils have been removed and where the surgical technique has been excellent and lymphoid regrowth occurs either in the tonsillar fossa or posterior pharynx, one must search for an allergic etiology.

This paper helps to settle one of the most confusing problems which confronts the practicing physician. Children are constantly having tonsillectomies done because of respiratory symptoms and in many cases their symptoms are not relieved by the procedure. Every physician who deals with children would do well to remember the absolute indications for tonsillectomy and to have the operation performed only if one or more of these is present but to search for the etiologic cause for the respiratory symptoms in those patients in whom the indications are not present.

Bentolila et al[9] in a discussion of allergic cataract report a case of juvenile cataract associated with atopic dermatitis. The cataract appears after dermatitis has been established and in the second or third decade of life or later. No definite explanation of the mechanism which causes the cataract is known.

Jaros et al[41] review the literature on thiamine intolerance and summarize in table form the 203 cases that have been reported during the last fifteen years. Among these, two were fatal. From the data in these papers, they conclude that the majority of toxic effects from thiamine occur in nonallergic individuals and therefore find it difficult to explain such reactions as caused by hypersensitivity alone. They also list series consisting of several thousand patients who have been repeatedly injected with thiamine without any toxicity or allergy being evident. They report two cases in which reactions were definitely due to thiamine. The physiology, chemistry

and pharmacology of thiamine are reviewed. They record experiments on dogs which indicate that the pharmacologic effects of thiamine are identified with acetylcholine and histamine and can be reversed by epinephrine. The authors conclude from the case reports and from experimental data that the weight of pharmacologic and even clinical evidence would indicate considerable doubt that allergy is the basis for thiamine intolerance. It is useless to perform any type of skin test as thiamine is a primary urticariogenic agent.

Dees and Simmons[21] review the question of allergy of the urinary tract. Their report includes both children and adults. They summarize the cases of urinary allergy reported in the literature. The symptoms of urinary allergy as reported involve the lower urinary tract with irritative symptoms in the urethra and bladder, and the upper urinary tract with ureteral or renal colic, hematuria or albuminuria. In the series reported, an allergic basis for lower urinary tract symptoms has been suggested in nineteen cases. Upper urinary tract symptoms of colic or spasm attributed to allergy have been described in ten patients. The upper urinary tract symptom of hematuria, painless in most instances, probably compatible with so-called essential hematuria, has been ascribed to allergy in eleven reported cases. They did not find any published reports of orthostatic albuminuria as a manifestation of allergy. Enuresis due to allergy was reported in 100 children and it was claimed that good results were obtained from allergic management. Other conditions of the urinary tract which have been ascribed to allergy are a type of acute allergic nephritis somewhat similar to acute glomerulonephritis, the nephrotic syndrome, Henoch-Schonlein purpura, favism with hematuria and paroxysmal hemoglobinuria. Ivy dermatitis has been reported as causing acute nephritis in seven cases and periarteritis nodosa in two. A few reported miscellaneous cases of other forms of allergy of the urinary tract are also included. A great many allergists were questioned regarding the incidence of allergic reactions in the urinary tract among their patients. Many believe that they had seen such patients, but none could supply thoroughly studied cases other than those already reported in the literature. The authors also reviewed the records of 613 patients seen at Duke Hospital with several urologic conditions whose etiology was not definitely established. Of these patients, allergy in other systems was found in 12 per cent of the group. Only six urinary conditions were studied. (1) essential hematuria (2) orthostatic albuminuria (3) enuresis (4) ureteral spasm (5) chronic trigonitis (6) urethritis and interstitial cystitis.

Orthostatic albuminuria: Eighty-two cases were studied. In none of these did allergic treatment seem to have any effect on the orthostatic albuminuria. The patients subjected to this treatment were the eighteen patients with a personal or family history of allergy.

Essential hematuria: Thirty-two patients were studied. There was a personal allergy in only five, only one of these had a major allergy and allergic management did not influence the bleeding.

Chronic, non-specific cystitis, trigonitis and urethritis: 300 patients were studied. Coexisting allergy was found in 11 per cent of the entire group.

Ureteral spasm, interstitial cystitis, and enuresis were not adequately worked up allergically.

In summary, they found that while a urinary tract allergy may occur, the literature contains few reports in which both an organic basis had been completely excluded and an allergic basis incontrovertably proved by the

diagnostic studies which were described. In their analysis were 613 patients with an allergy present in 12 per cent, which is the percentage accepted for the incidence of allergy in the general population. They did not feel justified in suspecting that allergy plays any role in these disorders.

Michael and Williams[51] report twenty children from the Neurological Clinic in a children's hospital and also in their private practice who had typical migraine. When first seen these children varied in age from six to fourteen years. These children were completely studied but only the allergic findings will be discussed here. In four families there were relatives with allergic disorders but in only two children in the series were allergic manifestations coexistent with the migraine. In spite of this low incidence of allergy in the series, the results of their treatment are interesting. In thirteen of the fifteen children who did not have convulsions, they used an antihistaminic given at the onset of the attack to avert the seizures. This proved to be a reasonably satisfactory way of treating these children, but the authors point out that it raises a question as to whether the effectiveness of these drugs is due to their antihistaminic properties or to their well-known sedative effect.

It is a common belief that migraine is an allergic disease; this small but carefully studied series does not confirm this impression. However, since migraine is relatively rare in children it is difficult to get a series large enough to arrive at any definite conclusions. Certainly, there are cases which respond to allergic management.

Davison[20] in a very exhaustive review of allergy of the nervous system, first reviews the literature concerning allergy of the nervous system in general and then discusses his own observations on allergy of the nervous system. He lists well over 100 neurologic manifestations which have been reported by himself and by others as having been proved to be caused by allergic sensitivity. The major portion of the article is concerned with epilepsy. The author reports sixty-seven patients which he has examined in his own office, fifty-two having attacks of petit mal or grand mal epilepsy and fifteen having evidence of disturbances of the central nervous system with attacks of unconsciousness but without convulsions. Of these patients, seven were in the first decade, nine in the second decade and the remainder of the patients went up to the eighth decade. Of the sixty-seven patients, eleven had satisfactory relief of the allergic manifestations and complete relief of cerebral symptoms and convulsions with the use of anti-allergic therapy but without the use of anticonvulsants. Twenty-three were markedly improved in that they had improvement of the allergic symptoms and improvement of the cerebral symptoms and convulsions following allergic treatment, which had not been previously obtained by general treatment, or by the use of various anticonvulsants alone. The remainder were unimproved. Of the patients proved sensitive to foods, many foods were implicated, milk in ten cases, chocolate in seven, eggs in five and wheat in three.

The next section deals with a questionnaire sent to physicians concerned with both allergy and epilepsy. Answers were received from 207, many of whom replied that they had not seen epilepsy due to allergy after long years of practice. However, fifty-seven physicians reported cases of epilepsy and/or cerebral allergy, relieved by allergic management. Foods were implicated as well as inhalants.

The next section is a review of the literature on the subject of epilepsy due to allergy. A great many reports are discussed, starting in 1919. In

these references twenty-two authors have reported forty-four cases of grand mal or petit mal epilepsy which were completely relieved by allergic management without the use of anticonvulsants. Foods were responsible in forty-one cases, one proved to be due to the inhalation of tobacco smoke, one to the inhalation of cat epithelia and one to tobacco chewing. In these forty-four patients attacks had been produced two or more times by exposure to the offending food, drug or inhalant. Davison feels that a great deal more has to be learned about the association of these two diseases and that adequate criteria should be drawn up for stating that a given case of epilepsy is due to allergy. He states that all epileptic cases with a family history of allergy or personal history of allergy should be examined from an allergic point of view. In the paper there is no indication as to how many of these cases were in children, but a great many were.

While it is out of the question to examine every epileptic child from an allergic point of view, this article demonstrates that all should be so examined if there is any hint from the history or physical examination that the convulsion may be on an allergic basis, because the prognosis in children having allergic convulsions is much better if they are given proper anti-allergic therapy.

Ratner[61] has edited a book on allergy in relation to pediatrics. This volume represents a panel discussion presented in co-operation with members of the Allergy Section of the American Academy of Pediatrics and under the auspices of the American College of Allergists at their Fifth Annual Convention. There are seventeen contributors and the book covers the field of pediatric allergy rather thoroughly.

Collins-Williams and Ratner[17] discuss Pediatric Respiratory Allergy in a round table discussion presented at the American Academy of Pediatrics Meeting in 1951.

Conn[18] in *Current Therapy* for 1952, includes a section on allergy which has been revised this year. Sixteen different authorities contribute to the therapy of allergic diseases, and there is included a formulary of prescriptions useful in the treatment of allergic dermatoses. There is also a list of drugs used in the therapy of allergic diseases with their doses and conversion factors.

Kallos[42] in *Progress in Allergy,* Vol. 3, includes a chapter on allergy in children by Murray Peshkin, who discusses the evaluation of diagnostic tests for sensitivity in infancy and the allergic syndromes which are seen in childhood.

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*1421 Danforth Ave., Toronto 6 (Dr. Collins-Williams)*
*50 E. 78th St., New York 21 (Dr. Ratner)*

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## AMERICAN MEDICAL ASSOCIATION
## SESSION ON ALLERGY

### Basildon Room of the Waldorf-Astoria

### Officers of Session

*Co-Chairmen*—Walter S. Burrage, Boston; J. Warrick Thomas, Richmond, Va.
*Secretary*—Alan G. Cazort, Little Rock, Ark.

### Wednesday, June 3—2:00 P.M.

The Use and Abuse of Cortisone and ACTH in Allergic Disease—Leon Unger, Chicago

Classification of Asthma—Oscar Swineford, Jr., Charlottesville, Va.

Allergic Noninfectious Pneumonitis in Incipient Asthma—George L. Waldbott, Detroit

Mechanism of Drug Reactions—Adolph Rostenberg, Jr., and James R. Webster, Chicago

### Clinical Panel

*Moderator*—Giles A. Koelsche, Rochester, Minn.

*Participants*—Walter S. Burrage, Boston; Samuel M. Feinberg, Chicago; Bret Ratner, New York; Harry L. Rogers, Philadelphia; Bram Rose, Montreal, Canada; J. Warrick Thomas, Richmond, Va.

# In Memoriam

## JACK COHN

### 1907-1953

Jack Cohn, A.B., M.D., was born in San Francisco, California, forty-six years ago. He was a graduate of Lowell High School, San Francisco, and received his Bachelor's degree from the University of California in 1928, and graduated from Stanford University Medical School in 1933. He served his internship at Mt. Zion Hospital, San Francisco, his residency at the San Francisco County Hospital and was later head resident at Cook County Hospital in Chicago. He took postgraduate training in 1934-35 at Northwestern University and served as Assistant to Dr. S. Feinberg. Later, in 1938, he became associated with Dr. George Piness and Dr. Hyman Miller, Los Angeles. He taught Pediatric Allergy at Stanford University from 1935 to 1938 and at Mt. Zion Hospital and San Francisco Out-Patient Department in Allergy from 1938 until recently when his illness forced him to curtail his activities. He also served as resident of the Illinois Ear and Eye Infirmary, Chicago, in 1935, and as visiting physician to San Francisco Children's Home and Orphanage from 1935 to 1938. Doctor Cohn served as Chief of Adult and Pediatric Allergy, Mt. Zion Hospital, from 1938 to the time of his death on January 2, 1953. He was a staff member of the Mt. Zion and Hahnemann Hospitals in San Francisco. He was the author of several articles on allergy in leading medical journals, and an active Fellow of the American College of Allergists.

Doctor Cohn had not been in good health for the past several years as the result of several coronary episodes and he was forced to restrict his activities considerably. He had many medical friends, and was greatly loved and respected by them as well as by his many patients. He had a keen interest in music and enjoyed playing the Hammond organ.

Doctor Cohn is survived by his wife, Barbara Prince Cohn, his mother, Mrs. Stella Cohn, and his sister, Mrs. Bertrand F. Lurie. His many friends extend their sincere sympathy.

## ROSE HERCHMAN KLEIN

### 1902-1953

Dr. Rose Herchman Klein died January 29, 1953, after an illness of several months' duration. Her loss will be keenly felt by both her professional colleagues and her patients. An unusually exacting physician, Dr. Klein practiced the specialty of allergy. Having an investigative mind, she brought the latest in medical research to the care of her patients.

Rose Herchman Klein was born in Hartford, July 8, 1902, daughter of the late Samuel and Pauline Waxman Herchman. She was graduated from Teachers College, Columbia University, and then served in the laboratory of the Hartford Hospital while Dr. Wilmer Allen was director of laboratories. It was at this time that she decided to fulfill her ambition to become a physician. She received her medical degree in 1940 from the Women's Medical College in Philadelphia. She interned at the Women's Hospital in Philadelphia and at Bellevue Hospital in New York City. She became a staff member in the department of allergy at the Mt. Sinai Hospital, New York, where she continued to serve until the onset of her illness. Subsequent to establishing her practice in Hartford, she became a staff member of the Mt. Sinai Hospital, Hartford. She was a member of the American College of Allergists

American Academy of Allergy, the Hartford County Medical Association, the Connecticut State Medical Society, and the American Medical Association.

Dr. Klein was a truly remarkable woman. She never permitted her illnesses to interfere with her medical activities. She endeavored successfully to keep concern of herself in the background. She was a modest and quiet woman who allowed her deeds to reflect her personality. During her final illness, her stoic resolve to live astounded the physicians and nurses with whom she came in contact.

Dr. Klein is survived by her husband, Abraham Klein, and a brother, George Herchman. Members of the College extend their sincere sympathy.

G. I. PITEGOFF, M.D.

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## Rh COUNTERSENSITIZATION

Following Unger's report on the apparent efficacy of bacterial vaccines in the prevention of sensitization to the Rh factor, an Rh countersensitization clinic was established at the United States Public Health Service Hospital, Staten Island, N. Y. All pregnant women found to be negative for the $Rh_0$ and rh′ factor were referred to this clinic. Vaccine therapy was started immediately, and then the presence or absence of sensitization and of $Rh_0$ and rh′ factors in the father was determined. Vaccine therapy consisted of six weekly injections of typhoid vaccine followed by six weekly injections of pertussis vaccine. This cycle was continued, with an increase in dosage at every change, until labor ensued. Sensitization to the Rh antigens was determined monthly until the thirty-fourth week of gestation and then every two weeks until parturition occurred. Of 211 referred pregnant women, eight were found to be sensitized before therapy was begun. In two of these patients with a suggestive previous history anti-Rh antibodies disappeared during therapy. Erythroblastosis occurred in the infants of six of the eight sensitized women in this series. Among the 203 mothers who were not sensitized before therapy and who delivered Rh-positive infants, not a single case of sensitization during therapy occurred. Available statistics indicate that twelve cases of erythroblastosis fetalis might have been predicted in this group. If the 314 patients studied by Unger are included, thirty-two cases of erythroblastosis would be expected. Instead of these thirty-two cases, there were only four cases of erythroblastosis in the infants of the combined series of nonsensitized mothers. This sharp reduction in the expected number of erythroblastotic infants is attributed to the use of bacterial vaccines. The most likely explanation for the mode of action of bacterial vaccines is provided by the "key enzyme" theory. This assumes that the antigen of the bacterial vaccine competes with the Rh antigen for enzymes that are required for the production or reaction of Rh antibodies. This prevents sensitization of the mother or the development of erythroblastosis in the fetus.—*Am. J. Obst. & Gynec., 64:1191-1420 (Dec.) 1952. Abstracted in J.A.M.A. (Mar. 14) 1953.*

# News Items

## SECOND EUROPEAN CONGRESS OF ALLERGY

Your attention is again called to the Second European Congress of Allergy, which will be held in Copenhagen, Denmark, from May 20 to 23, 1953. This Congress is being held under the auspices of the International Association of Allergology and assumes international importance. The preliminary program announces lectures by many European authorities and the subjects cover a wide scope. It is earnestly hoped that members in North America and South America will plan to attend.

### Officers of the Congress

Ernst B. Salén, M.D., Stockholm, President
Professor Poul Bonnevie, M.D., Copenhagen, I. Vice President
Egon Bruun, M.D., Copenhagen, Secretary General
Michael Schwartz, M.D., Copenhagen, Secretary

### Congress Committee

Dr. Erik Andersson, Copenhagen
Kaj Baagøe, M.D., Kolding
M. Bjørneboe, M.D., Copenhagen
Professor P. Bonnevie, M.D., Copenhagen
Egon Bruun, M.D., Copenhagen
Professor K. Brøchner-Mortensen, M.D., Copenhagen
P. J. Dragsted, M.D., Copenhagen
Chr. Hamburger, M.D., Copenhagen

There will be luncheons, and on Friday, May 22, the Official Banquet will be held. Ladies attending the Congress are cordially invited to the Opening Ceremony and the Reception following it. A special ladies' program will be arranged. Congress Fee: 50 Danish Crowns. Ladies attending the Congress: 25 Danish Crowns. Official Banquet: 30 Danish Crowns.

## INHUMANITY VERSUS HUMANITY

Of interest to all allergists are the following remarks made by Dr. Robert Gesell, Professor of Physiology, University of Michigan, Ann Arbor, Michigan. Since practically all fundamental investigations in allergy are performed on the lower animal, it is imperative that attention be called to the disturbing situation created by the National Society for Medical Research.

"On February 25, 1952, I called attention to recent abuses in animal experimentation published in *The Lancet*. On April 15, I addressed the American Physiological Society on the same subject.

"The National Society for Medical Research has taken issue with both statements and, in its letter of September 17, 1952, to the members of the Federation, stated that 'Dr. Gesell's charges covered seven broad points.'

"These points inevitably resolve themselves into but one issue—Inhumanity versus Humanity. I thought this idea was clearly stated in my remarks of April 15 which follow:

"The National Society for Medical Research would have us believe that there is an important issue in vivisection versus antivivisection.

"To a physiologist there can be no issue on vivisection per se.

"The real and urgent issue is humanity versus inhumanity in the use of experimental animals.

"But the NSMR attaches a stigma of antivivisection to any semblance of humanity.

"Antivivisection is their indispensable bogie which must be kept before the public at any cost.

"It is their only avenue towards unlimited procurement of animals for unlimited and uncontrolled experimentation.

"The NSMR has had but one idea since its organization, namely—to provide an inexhaustible number of animals to an ever growing crowd of career scientists with but little biological background and scant interest in the future of man.

"Consider what we are doing in the name of science, and the issue will be clear.

"We are drowning and suffocating unanaesthetized animals—in the name of science.

"We are determining the amount of abuse that life will endure in unanesthetized animals—in the name of science.

"We are producing frustration ulcers in experimental animals under shocking conditions—in the name of science.

"We are observing animals for weeks, months or even years under infamous conditions—in the name of science.

"Yet it is the National Society for Medical Research and its New York satellite that are providing the means to these ends.

"And how is this being accomplished?

"By undermining one of the finest organizations of our country: The American Humane Society.

"With the aid of the halo supplied by the faith of the American people in medical science, the N.S.M.R. converts sanctuaries of mercy into animal pounds at the beck and call of experimental laboratories regardless of how the animals are to be used.

"What a travesty of humanity!

"This may well prove to be the blackest spot in the history of medical science."

* * *

Those who are further interested should read "Seizure Laws" by Mel L. Morris, Executive Director, American Humane Association. Reprints may be obtained from the National Humane Review, 135 Washington Avenue, Albany 10, New York. This article presents the opinion of the American Humane Association under attack by the National Society for Medical Research.

## FIRST WESTERN HEMISPHERE CONFERENCE

Men from a dozen medical colleges and a score of specialties will report the latest developments from the frontiers of medicine to the First Western Hemisphere Conference of the World Medical Association at Richmond, Va., on April 24. Participants will represent the leading medical schools of this country and Latin America.

## REPORT ON POLLEN SURVEY

Report of the Pollen Survey Committee of the American Academy of Allergy for 1952 has been received, together with a booklet, "Hay Fever Holiday" revised January, 1953, by The Pollen Survey Committee Council on Aeroallergens of the American Academy of Allergy. Dr. Oren C. Durham of the Abbott Laboratories is Chairman of this Committee. There are two very excellent tables, one on "Current and Comparative Ragweed Pollen Data" from all active Committee members reporting during 1952, composed of seventy members. A second table is, "Condensed Full-Season Pollen Reports for 1952." If the members of the Academy have not received their copy, please send for it.

## FELLOWSHIP IN ALLERGY

Northwestern University Medical School offers a Fellowship in Allergy designed to provide training and experience for specialization. This Fellowship is approved by the AMA Council on Medical Education and Hospitals, is accredited by the Board of Internal Medicine for credit toward the formal training requirements of the Board, and is approved for training by the Sub-Specialty Board in Allergy. An annual stipend of $2,500-$3,600 is offered.

Inquiries should be addressed to Samuel M. Feinberg, M.D., Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11, Illinois.

## SYMPOSIUM ON AIR POLLUTION AND ITS CONTROL

A very successful and well-attended Symposium on Air Pollution and Its Control, was sponsored by the Department of Bacteriology and Public Health of Wagner College, Staten Island, New York, on March 7, 1953.

Papers by experts on air pollution covering a broad range of subjects were given: Physics of Air Pollution, Aerodynamic Factors in Air Pollution, Appraisal of Atmospheric Pollution Problems, Air Pollution and Its Effects on Health, Effects of Air Pollution on Vegetation, Analogy of Interstate Water and Air Pollution Problems, Contributions of Industry to Air Pollution Control, Air Pollution Control by Municipal Agencies, State Control of Air Pollution.

## SOUTHEASTERN ALLERGY ASSOCIATION

The Southeastern Allergy Association will meet at the Andrew Jackson Hotel, Nashville, Tennessee, May 15 and 16. A clinic, with patients from the Vanderbilt Medical School, will be conducted by Dr. Clarence Thomas and Dr. James Overall. Dr. Murray Peshkin, President-Elect of the American College of Allergists, and Dr. Ben Rappaport, President of the American Academy of Allergy, will be guest speakers. There will be a symposium on Mental and Emotional Aspects of Allergy with Dr. Hal Davison as moderator. Papers will be presented by Dr. Marion Davidson, Birmingham, Alabama and Dr. Charles Wofford of Johnson City, Tennessee.

## SOCIEDAD CUBANA DE ALERGIA

Officers for the present year of the Sociedad Cubana de Alergia are as follows:
President—Dr. José Joaquin Pedrera.
Vice President—Dr. José M. Quintero Fosaas.
Secretary—Dr. Fermín Alpízar.
Treasurer—Dr. G. Estrada de la Riva.
Board Member—Dr. Julio de los Santos.
Board Member—Dr. José Cadrecha.
Board Member—Dr. Josefina Amiguet.

## PHILADELPHIA ALLERGY SOCIETY

The following are the newly elected officers for the year 1953 of the Philadelphia Allergy Society:
President—Howard C. Leopold, M.D.
Vice President—George W. Truitt, M.D.
Secretary-Treasurer—Edmund E. Ehrlich, M.D.

## NEWS ABOUT ACA MEMBERS

Dr. Coleman Harris, 2600 Alameda Street, Vallejo, California, a Fellow of the American College of Allergists, has assumed the practice of the late Dr. Jack Cohn.

* * *

Dr. Leon Unger has returned from an around the world trip. During this time, he delivered seventeen speeches before various medical societies in Hawaii, Japan, Hong Kong, Siam, Pakistan; Calcutta, New Delhi and Poona in India; Haifa and Jerusalem in Israel; and Athens, Greece.

Many of these meetings were held under the auspices of the American College of Chest Physicians, and the subjects covered were various aspects of bronchial asthma and migraine.

# BOOK REVIEWS

CLINICAL ALLERGY. By French K. Hansel, M.D., Director, Hansel Foundation for Education and Research in Allergy; Chief of Allergy Service, DePaul Hospital, St. Louis. 1005 pages, 86 illustrations and 3 color plates. St. Louis: The C. V. Mosby Co., 1953. Price $17.50.

It is not often that one has the privilege of reading a text in allergy which is as stimulating as the volume compiled by Dr. Hansel after decades of leadership in the field of clinical allergy. This leadership was not expressed along the narrow lines of skin tests and injections which have too often been confused with the real study of the allergic patient. Dr. Hansel from the beginning recognized the need for an integrated approach. His experiences in allergy of the nose and its sinuses, in otolaryngology in general, supplemented by a pioneering spirit in the study of antigen-antibody reactions as applied to ophthalmologic, pediatric, and dermatologic allergy make this volume especially important. This volume is presented in so practical a fashion that the general practitioner can easily utilize the subject matter. Five chapters are devoted to the special problems in allergy as related to infants and children. Antibodies, antihistamines, aerosols, ACTH and Cortisone are treated in detail. Methods of therapy of urticaria, eczema, bacterial allergy, migraine, histamine, headache, and cardiovascular allergy are part of this extensive treatment.

Although Dr. Hansel's method of using small doses is not accepted by all of those active in the practice of allergy, there is no doubt in the mind of the reviewer that the use of high doses recommended by some allergists is unwarranted by either the scientific or the clinical data now available. The reviewer is inclined to accept the point of view of Dr. Hansel that the principle of the "small or optimum dosage" represents an interesting as well as safe procedure. It is an important advance in certain types of therapy which are not unknown in other immunization technics. Those who employ large and at times anaphylactoid dosage should bear in mind the findings of Castberg and Schwartz. They reported† that in young patients with hay fever, after administration of shocking doses of pollen extract, important changes occurred in the electrocardiogram. In all cases, changes typical for anoxemia of the myocardium were found. This raises many questions. What, for example, is the effect of overdosage over prolonged periods, for many years? Do the doses producing subclinical shock in the tissues lead to chronic changes due to therapy? To avoid overdosage, the local reaction of the patient's skin during therapy as well as general reactions are the guide to therapy, rather than any particular number of units advocated for a given patient in a routine fashion. The psychologic implications in the administration of subanaphylactic doses include a threat to the patient of anaphylactic shock and its consequences. This is unwarranted by any increased value in therapeutic results attained. Small doses without the dangers of anaphylaxis have in the reviewer's experience provided adequate protection. The above notations on pollen extract apply equally to other specific allergenic extracts and nonspecific preparations.

In 1000 pages of well-printed text the subject of allergy is divided into fifty-three chapters, each of which reflects the erudition of the author. There is an index of more than twenty-seven pages. The method of presentation is characterized by clarity. This clarity is found in the entire organization of the book in such a fashion that this book can truly be called the best text on general clinical allergy now available.

H.A.A.

†Castberg, T., and Schwartz, M.: Changes in electrocardiogram during allergic shock. Acta med. scandinav., 126:459, 1947.

PARDON MY SNEEZE. By Milton Millman, M.D., San Diego. 217 pages, 8 illustrations and a number of cartoons. San Diego: Fry & Smith, Ltd., 1952. Price cloth bound $3.50; paper bound $2.00.

As the title indicates, this monograph is written for the layman. It contains twenty-seven chapters, in three parts, and a number of cartoons.

Part One is devoted to describing allergy and the allergic mechanism, rough outlines of case histories are used to illustrate certain conditions, the manner of making allergy tests is described, treatment roughly outlined, and a number of proprietary drugs are listed.

Part Two is best explained by the author's statement that "This monograph is not intended to make the layman a diagnostician." It attempts to give the patient an idea of the whys and wherefores of hay fever, asthma, eczema and allergies, including a summary of instructions for parents of children with eczema.

Part Three gives sources of contacts of various allergens, methods of elimination, the value of keeping a diary, and methods to assist the family to remove all causative allergenic agents from the environment. Chapters 22 through 27 contain a number of recipes which may be of use to the allergic patient. It can be recommended for your allergy patients.

This is an inexpensive monograph printed in fairly large type.

CURRENT THERAPY, 1953. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D., 835 pages. Price $11.00. Philadelphia: W. B. Saunders, 1953.

Many important additions have been made to this volume, which contains methods by 209 new contributors. Again the contributing editors have set down their present methods of treatment in brief, original discussions in exact detail necessary for proper management of the disease, and the latest accepted therapy is included. Diagnosis, unless it is an integral part of the therapy, is not discussed. It is assumed that an accurate diagnosis will be made before treatment is initiated. Some valuable information from the previous volume is necessarily repeated with only slight modification. It is obvious that radical changes in the therapy of certain diseases will not take place each year, but it should be of interest to the physician to know whether the therapy has or has not been changed.

There are sixteen sections, including the appendices and index. The sections embrace the infectious, venereal, and allergic diseases; diseases of the respiratory, cardiovascular, digestive, endocrine, urogenital, nervous and locomotor systems; diseases of the blood and spleen, metabolism, and skin; obstetric and gynecologic conditions; diseases due to physical and chemical agents.

The therapy of the allergic diseases is written by nineteen authorities in their respective fields in allergy, including allergy in children, anaphylaxis and serum sickness, antihistamines in the treatment of allergy, bronchial asthma, allergic dermatitis, drug allergy, endocrine allergy, food allergy, genitourinary allergy, nasal allergy, ocular allergy, and production of an "allergen-free" environment. The appendices and index include a roster of drugs, dosages, conversion factors, tables for making percentage solutions and a complete index.

This volume is a ready, authoritative reference covering the whole field of current therapy. It is attractively printed and bound.